

10/677,956

Attorney Docket No. 323-100US-D



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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ZEBEDEE et al.)	Examining Attorney:
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For: METHODS AND SYSTEMS FOR)	
PRODUCING RECOMBINANT)	
VIRAL ANTIGENS)	

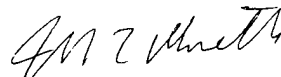
**EXHIBIT 1 TO THE
DECLARATION OF JOSEPH E. MUETH**

Commissioner for Patents
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Attached hereto as Exhibit 1 to the Declaration of Joseph E. Mueth is United
States Patent Application Serial No. 08/272,271.

Date: February 13, 2006

Respectfully submitted,


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THOMSON

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SUBCLASS

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GROUP ART UNIT

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EXAMINER

Wortman

APPLICANTS
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MARC S. NASOFF, SAN DIEGO, CA; ALFRED M. PRINCE, NEW YORK, NY.

CONTINUING DATA***

VERIFIED

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TITLE
NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES

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SUZANNE ZEBEDEE, SAN DIEGO, CA; GENEVIEVE INCHAUSPE, NEW YORK, NY; MARC S. NASOFF, SAN DIEGO, CA; ALFRED M. PRINCE, NEW YORK, NY.

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NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES

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PARTS OF APPLICATION FILED SEPARATELY NOTICE OF ALLOWANCE MAILED PREPARED FOR ISSUE CLAIMS ALLOWED Total Claims Print Claim ISSUE FEE Amount Due Date Paid DRAWING Sheets Drwg. Figs. Drwg. Print Fig. Primary Examiner ISSUE CLASSIFICATION Class Subclass ISSUE BATCH NUMBER Label Area WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 388. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

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CONTENTS

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1. Application _____ papers.
2. 2th. re DNA Sequence 12/31/90
3. 2th. re Unsigned Decl. 12/31/90
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5. Decl. + Surcharge 02-25-91
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8. Rep. 30 days 12/17/91
9. Collectiv 1/17/92 12/16
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12. Amdt B + prior art 7-20-92 Conf
13. Rej 3 mos 10/5/92 9-28
14. Ext of time 1 month 2-1-93
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16. Declaration 2-1-93
17. Disclosure Statement 2-1-93
18. Interview Summary 2/23/93
19. Suppl. response 2-16-93
20. Suppl. Req. For Recon. 4-22-93
21. Final Rejection 7-12-93 7/12
22. Amdt D (NE) 10-14-93 10-14-93
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25. Ext of time 3 mos 1-13-94
26. Notice of appeal 1-13-94
27. Ext of time 2-8-94 2/8
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1. Application _____ papers.

2. ~~27~~ ²⁷ Pet. Grant E

7/8/94

3. ~~28~~ ²⁸ Disclosure, Stmt

10/11/94

4. ~~29~~ ²⁹ Law Sec Listing (OK)

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5. ~~30~~ ³⁰ Reg 3 mos

3-21-95 3/20

6. ~~31~~ ³¹ Reg time (3 mos)

9/22/95 w/m 9/25

7. ~~32~~ ³² Amdt 3

9/22/95

8. ~~33~~ ³³ Fin Reg 3 mos

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9. ~~34~~ ³⁴ Amdt P/A

4-22-96

10. ~~35~~ ³⁵ Change of Address

4-22-96

11. ~~36~~ ³⁶ Reg Records under 1.129(a)

4/25/96 w/m 4/22

12. ~~37~~ ³⁷ Rejection (final)

8-6-96 8/5

13. ~~38~~ ³⁸ Reg Records

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16. ~~41~~ ⁴¹ Power to Inspect

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17. ~~42~~ ⁴² Ext. of time 3 mos / notice of appeal

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20. ~~45~~ ⁴⁵ Ext. of time 1 mo

9/18/97

21. ~~46~~ ⁴⁶ Notice of Defective Appeal Brief

2-3-98

22. ~~47~~ ⁴⁷ Request for Access

2-3-98

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SEARCHED

Class	Sub.	Date	Exmr.
435	5	4/3/92	Dew
436	820 828		
Updated		9/21/92	Dew
Updated		7/6/93	Dew

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	Date	Exmr.
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Updated 7/6/93	7/6/93	Dew

INTERFERENCE SEARCHED

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Class	Sub.	Date	Exmr.
435	5	3/10/95	Dw
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All updated Dw parent			
Updated		1/18/96	Dw
Updated		7/25/96	Dw
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	Date	Exmr.
Revised parent 07/616369	3/10/95	Dw
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INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

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VERIFIER	364	6/26/91
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SYMBOLS

- ✓ Rejected
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- Restricted
- N Non-elected
- I Interference
- A Appeal
- O Objected

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POSITION	ID NO.	DATE
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EXAMINER	422	8/3
TYPIST	21	8/8/94
VERIFIER	1236	8/10/94
CORPS CORR.		
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INDEX OF CLAIMS

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SYMBOLS

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PATENT APPLICATION SERIAL NO. 07 616369

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PATENT AND TRADEMARK OFFICE
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07/616,369		11/21/90	435	1802			
APPLICANT	SUZANNE ZEBEDEE, SAN DIEGO, CA; GENEVIEVE INCHAUSPE, NEW YORK, NY; MARC S. NASOFF, SAN DIEGO, CA; ALFRED M. PRINCE, NEW YORK, NY.						
	CONTINUING DATA*** VERIFIED THIS APPLN IS A CIP OF 07/573,643 08/25/90 ABN						
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TITLE	NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES						
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Date	Certifying Officer						

ABSTRACT

5 The present invention relates to a DNA segment encoding a recombinant non-A, non-B hepatitis structural protein or fusion protein and a recombinant DNA (rDNA) molecule capable of expressing either protein. Cells transformed with the rDNA, methods for producing the proteins in addition to compositions containing the proteins, and their use in diagnostic methods and systems, and in vaccines are also described.



RB LABEL NO. 1877 229

66-101-A

501

NON-A, NON-B HEPATITIS VIRUS ANTIGEN,
DIAGNOSTIC METHODS AND VACCINES

07 616369

Cross Reference to a Related Application

5

This is a continuation-in-part application of copending application Serial Number 07/573,643, filed August 25, 1990, the disclosures of which are hereby incorporated by reference.

10

Description

Technical Field

15

The present invention relates to a segment of deoxyribonucleic acid (DNA) that encodes a non-A, non-B hepatitis structural protein and a recombinant DNA (rDNA) that contains the DNA segment. Cells transformed with a rDNA of the present invention and methods for producing the NANBV structural protein are also contemplated. The invention also describes compositions containing the NANBV structural protein useful in diagnostic methods and in vaccines.

20

Background of the Invention

25

Non-A, non-B hepatitis (NANBH) is believed to be caused by a transmissible virus that has been referred to as both hepatitis C virus (HCV) and non-A, non-B hepatitis virus (NANBV). Although the transmissible disease was discovered years ago, a complete characterization of the causative agent is still being developed.

30

An isolate of NANBV has been obtained and portions of the viral genome were molecularly cloned and sequenced. Choo et al, Science, 244:359-362 (1989). Additional strains of NANBV were isolated and their genomes were partially characterized at the nucleotide sequence level. The similarities in

35

nucleotide base sequence between these isolates of NANBV suggest that they are a part of a family of related viruses. Okamoto et al, Japan J. Exp. Med., 60:163-177 (1990). Properties of the NANBV genome suggest that NANBV may be a very distant relative of the flavivirus family. However, similarities in both the size and hydropathicity of the structural proteins suggest that NANB viruses may also be distantly related to the pestivirus family. Miller et al, Proc. Natl. Acad. Sci., 87:2057-2061 (1990); and Okamoto et al, Japan J. Exp. Med., 60:163-177 (1990).

The difficulties in characterizing the NANBV isolates taxonomically, the lack of information regarding the proteins encoded by the NANBV genome, have made it difficult to identify relevant gene products useful for diagnostic markers and for producing NANBV vaccines.

The NANBV genome is comprised of a plus strand RNA molecule that codes for a single polyprotein. The gene products of NANBV are believed to include both structural and nonstructural proteins, based on homologies to characterized, related viruses. From these homologies, it is predicted that NANBV expresses a single polyprotein gene product from the complete viral genome, which is then cleaved into functionally distinct structural and nonstructural proteins. This type of viral morphogenesis precludes positive identification of the individual mature viral proteins until they have been physically isolated and characterized. Since no in vitro culturing system to propagate the virus has been developed for NANBV, no NANBV structural or nonstructural gene products (proteins) have been isolated from biological specimens or NANBV-infected cells. Thus, the identification of NANBV proteins, of their role in the viral life cycle, and of their role in disease,

have yet to be determined. In particular, antigenic markers for NANBV-induced disease have yet to be fully characterized.

5 Only one NANBV gene product, namely the antigen C-100-3, derived from portions of the nonstructural genes designated NS3 and NS4, has been expressed as a fusion protein and used to detect anti-C-100-3 antibodies in patients with various forms of NANB hepatitis. See, for example, Kuo et al, Science, 10 244:362-364 (1989); and International Application No. PCT/US88/04125. A diagnostic assay based on C-100-3 antigen is commercially available from Ortho Diagnostics, Inc. (Raritan, N.J.). This C-100-3 assay currently represents the state of the art in detecting 15 NANBV infections. However, the C-100-3 antigen-based immunoassay has been reported to preferentially detect antibodies in sera from chronically infected patients. C-100-3 seroconversion generally occurs from four to six months after the onset of hepatitis, and in some 20 cases C-100-3 fails to detect any antibody where an NANBV infection is present. Alter et al, New Eng. J. Med., 321:1538-39 (1989); Alter et al, New Eng. J. Med., 321:1494-1500 (1989); and Weiner et al, Lancet, 335:1-3 (1990). McFarlane et al, Lancet, 335:754-757 25 (1990), described false positive results when the C-100-3-based immunoassay was used to measure antibodies in patients with autoimmune chronic active hepatitis. In addition, Grey et al., Lancet, 335:609-610 (1990), describe false positive results using C-100-3-based 30 immunoassay on sera from patients with liver disease caused by a variety of conditions other than NANBV.

A NANBV immunoassay that could accurately detect seroconversion at early times after infection, or that could identify an acute NANBV infection, is not 35 presently available.

Summary of the Invention

The Hutchinson strain (Hutch) of non-A, non-B hepatitis virus (NANBV) has been propagated through passage in animals and portions of the virus have been
5 cloned and sequenced. Sequence data shows differences at both the nucleotide and amino acid level when compared to any previously reported NANBV strains. See, for comparison, Okamoto et al, Japan J. Exp. Med., 60:163-177 (1990); and International Application
10 No. PCT/US88/04125.

The identified sequences have been shown herein to encode structural proteins of NANBV. The NANBV structural proteins are also shown herein to include antigenic epitopes useful for diagnosis of antibodies
15 immunoreactive with structural proteins of NANBV, and for use in vaccines to induce neutralizing antibodies against NANBV.

The nucleotide sequence that codes for the amino terminal polyprotein portion of the structural genes
20 of the Hutch strain of NANBV is contained in SEQ. ID NO. 1. By comparison to putative relatives of NANBV, namely to other NANBV isolates, to flavivirus, and to pestivirus, the nucleotide sequence contained in SEQ. ID NO. 1 is believed to encode structural proteins of
25 NANBV, namely capsid and portions of envelope.

The structural antigens described herein are present in the putative capsid protein contained in SEQ. ID NO. 1 from amino acid residue positions 1-120, and are present in the amino terminal portion of the
30 putative envelope protein contained in SEQ. ID NO. 1 from residue positions 121-326.

The present invention contemplates a DNA segment encoding a NANBV structural protein that comprises a NANBV structural antigen, preferably capsid antigen.
35 A particularly preferred capsid antigen includes an amino acid residue sequence represented by SEQ. ID NO.

1 from residue 1 to residue 20, from residue 21 to
residue 40, from residue 2 to residue 40, or from
residue 1 to residue 74, and the DNA segment
preferably includes the nucleotide base sequence
represented by SEQ. ID NO. 1 from base position 1 to
base position 60, from base position 61 to base
position 120, from base position 4 to base position
120, or from base position 1 to base position 222,
respectively.

Also contemplated is a recombinant DNA molecule
comprising a vector, preferably an expression vector,
operatively linked to a DNA segment of the present
invention. A preferred recombinant DNA molecule is
pGEX-3X-690:691, pGEX-3X-690:694, pGEX-3X-693:691,
pGEX-3X-15:17, pGEX-3X-15:18, pGEX-2T-15:17, pGEX-2T-
CAP-A, pGEX-2T-CAP-B or pGEX-2T-CAP-A-B.

A NANBV structural protein is contemplated that
comprises an amino acid residue sequence that defines
a NANBV structural antigen, preferably a capsid
antigen, and more preferably one that includes the
amino acid residue sequence contained in SEQ. ID NO. 1
from residue 1 to residue 20, from residue 21 to
residue 40, from residue 2 to residue 40, or from
residue 1 to residue 74. Fusion proteins comprised of
a NANBV structural protein of this invention are also
contemplated.

Further contemplated is a culture of cells
transformed with a recombinant DNA molecule of this
invention and methods of producing a NANBV structural
protein of this invention using the culture.

Also contemplated is a composition comprising
NANBV structural protein. The composition is
preferably characterized as being essentially free of
(a) procaryotic antigens, and (b) other NANBV-related
proteins.

Still further contemplated is a diagnostic system in kit form comprising, in an amount sufficient to perform at least one assay, a NANBV structural protein composition of this invention, as a separately packaged reagent.

In another embodiment, the present invention contemplates a diagnostic system, in kit form, comprising a fusion protein of this invention. Preferably, the diagnostic system contains the fusion protein affixed to a solid matrix.

Further contemplated is a method of assaying a body fluid sample for the presence of antibodies against at least one of the NANBV structural antigens described herein. The method comprises forming an immunoreaction admixture by admixing (contacting) the body fluid sample with a fusion protein of this invention. The immunoreaction admixture is maintained for a time period sufficient for any of the antibodies present to immunoreact with the fusion protein to form an immunoreaction product, which product, when detected, is indicative of the presence of anti-NANBV structural protein antibodies. Preferably, the fusion protein is affixed to a solid matrix when practicing the method.

In another embodiment, this invention contemplates a vaccine comprising an immunologically effective amount of a NANBV structural protein of this invention in a pharmaceutically acceptable carrier. The vaccine is essentially free of (a) procaryotic antigens, and (b) other NANBV-related proteins.

A prophylactic method for treating infection, which method comprises administering a vaccine of the present invention, is also contemplated.

Detailed Description of the Invention

A. Definitions

Amino Acid: All amino acid residues identified herein are in the natural L-configuration. In keeping with standard polypeptide nomenclature, J. Biol. Chem., 243:3557-59, (1969), abbreviations for amino acid residues are as shown in the following Table of Correspondence:

TABLE OF CORRESPONDENCE

	SYMBOL		AMINO ACID
	1-Letter	3-Letter	
10	Y	Tyr	L-tyrosine
	G	Gly	glycine
	F	Phe	L-phenylalanine
	M	Met	L-methionine
	A	Ala	L-alanine
15	S	Ser	L-serine
	I	Ile	L-isoleucine
	L	Leu	L-leucine
	T	Thr	L-threonine
	V	Val	L-valine
20	P	Pro	L-proline
	K	Lys	L-lysine
	H	His	L-histidine
	Q	Gln	L-glutamine
	E	Glu	L-glutamic acid
25	W	Trp	L-tryptophan
	R	Arg	L-arginine
	D	Asp	L-aspartic acid
	N	Asn	L-asparagine
	C	Cys	L-cysteine

30

It should be noted that all amino acid residue sequences, typically referred to herein as "residue sequences", are represented herein by formulae whose left to right orientation is in the conventional direction of amino-terminus to carboxy-terminus.

35

Antigen: A polypeptide or protein that is able

to specifically bind to (immunoreact with) an antibody and form an immunoreaction product (immunocomplex). The site on the antigen with which the antibody binds is referred to as an antigenic determinant or epitope.

5 Nucleotide: a monomeric unit of DNA or RNA consisting of a sugar moiety (pentose), a phosphate, and a nitrogenous heterocyclic base. The base is linked to the sugar moiety via the glycosidic carbon (1' carbon of the pentose) and that combination of
10 base and sugar is a nucleoside. When the nucleoside contains a phosphate group bonded to the 3' or 5' position of the pentose it is referred to as a nucleotide. A sequence of operatively linked nucleotides is typically referred to herein as a "base
15 sequence", and is represented herein by a formula whose left to right orientation is in the conventional direction of 5'-terminus to 3'-terminus.

Base Pair (bp): A partnership of adenine (A) with thymine (T), or of cytosine (C) with guanine (G)
20 in a double stranded DNA molecule.

B. DNA Segments

 In living organisms, the amino acid residue sequence of a protein or polypeptide is directly related via the genetic code to the deoxyribonucleic
25 acid (DNA) sequence of the structural gene that codes for the protein. Thus, a structural gene can be defined in terms of the amino acid residue sequence, i.e., protein or polypeptide, for which it codes.

 An important and well known feature of the
30 genetic code is its redundancy. That is, for most of the amino acids used to make proteins, more than one coding nucleotide triplet (codon) can code for or designate a particular amino acid residue. Therefore, a number of different nucleotide sequences may code
35 for a particular amino acid residue sequence. Such nucleotide sequences are considered functionally

equivalent since they can result in the production of the same amino acid residue sequence in all organisms. Occasionally, a methylated variant of a purine or pyrimidine may be incorporated into a given nucleotide sequence. However, such methylations do not affect the coding relationship in any way.

In one embodiment the present invention contemplates an isolated DNA segment that comprises a nucleotide base sequence that encodes a NANBV structural protein comprising a NANBV structural antigen such as a capsid antigen, an envelope antigen, or both. Preferably, the structural antigen is immunologically related to the Hutch strain of NANBV.

More preferably, the encoded NANBV structural antigen has an amino acid residue sequence that corresponds, and preferably is identical, to the amino acid residue sequence contained in SEQ. ID NO. 1.

In one embodiment, the putative capsid antigen includes an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20, from residue 21 to residue 40, from residue 2 to residue 40, or from residue 1 to residue 74. In another embodiment, the capsid antigen includes the sequence contained in SEQ. ID NO. 1 from residue 69 to residue 120.

In another embodiment, the putative envelope antigen includes an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 121 to residue 176 or from residue 121 to residue 326.

Preferred DNA segments include a base sequence represented by the base sequence contained in SEQ. ID NO. 1 from base position 1 to base position 222, from base position 205 to base position 360, from base position 361 to base position 528, or from base position 361 to base position 978.

In preferred embodiments, the length of the nucleotide base sequence is no more than about 3,000 bases, preferably no more than about 1,000 bases. *12 bases 300 bases*

The amino acid residue sequence of a particularly preferred NANBV structural protein is contained in SEQ. ID NO. 2 from residue 1 to residue ³¹⁶315, (in SEQ. ID NO. 3 from residue 1 to residue 252, in SEQ. ID NO. 4 from residue 1 to residue 252 and in SEQ. ID NO. 6 from residue 1 to residue 271.) *new*

A purified DNA segment of this invention is substantially free of other nucleic acids that do not contain the nucleotide base sequences specified herein for a DNA segment of this invention, whether the DNA segment is present in the form of a composition containing the purified DNA segment, or as a solution suspension or particulate formulation. By substantially free is means that the DNA segment is present as at least 10% of the total nucleic acid present by weight, preferably greater than 50%, and more preferably greater than 90% of the total nucleic acid by weight.

In another embodiment, a DNA segment of this invention contains a nucleotide base sequence that defines a structural gene capable of expressing a fusion protein. The phrase "fusion protein" refers to a protein having a polypeptide portion operatively linked by a peptide bond to a second polypeptide portion defining a NANBV structural antigen as disclosed herein.

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A preferred first polypeptide portion has an amino acid residue sequence corresponding to a sequence as contained in SEQ. ID NO. 2 from about residue 1 to about residue 221, and is derived from the protein glutathione-S-transferase (GST).

A preferred second polypeptide portion defining a NANBV structural antigen in a fusion protein includes

an amino acid residue sequence represented by the sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20, ^{new} from residue 21 to residue 40, ^{new} from residue 2 to residue 40, from residue 1 to residue 74, from residue 69 to residue 120, from residue 121 to residue 176, or from residue 121 to residue 326.

In one embodiment, a fusion protein can contain more than one polypeptide portion defining a NANBV structural antigen, as for example the combination of two polypeptide portions representing different structural antigens as shown by the sequence contained in SEQ. ID NO. 1 from residue 1 to residue 120, or in SEQ. ID NO. 1 from residue 1 to residue 326.

In particularly preferred embodiments, that portion of a fusion protein encoding DNA segment of this invention that codes for the polypeptide portion defining a NANBV capsid antigen includes a nucleotide base sequence corresponding to a sequence that codes for an amino acid residue sequence as contained in SEQ. ID NO. 1 (from residue 1 to residue 20, from residue 21 to residue 40, from residue 2 to residue 40,) or from residue 1 to residue 74, and more preferably includes a nucleotide base sequence corresponding to a base sequence as contained in SEQ. ID NO. 1 from (base 1 to base 60, from base 61 to base 120, from base 4 to base 120,) or from base 1 to base 222, respectively.

In another embodiment, that portion of a fusion protein-encoding DNA segment of this invention that codes for the polypeptide portion defining a NANBV envelope antigen includes a nucleotide base sequence corresponding to a sequence that codes for an amino acid residue sequence as contained in SEQ. ID NO. 1 from residue 121 to residue 176 or from residue 121 to residue 326, and more preferably includes a nucleotide base segment corresponding in base sequence to the

sequence contained in SEQ. ID NO. 1 from base 361 to base 528 or from base 361 to base 978, respectively.

5 A particularly preferred fusion protein encoding DNA segment of this invention has a nucleotide base sequence corresponding to the sequence contained in SEQ. ID NO. 2 from base 1 to base 945, (SEQ. ID No. 3 from base 1 to base 756, SEQ. ID NO. 4 from base 1 to base 756, and SEQ. ID NO. 6 from base 1 to base 813.)

10 x In preferred embodiments, a DNA segment of the present invention is bound to a complimentary DNA segment, thereby forming a double stranded DNA segment. In addition, it should be noted that a double stranded DNA segment of this invention preferably has a single stranded cohesive tail at one or both of its termini.

15 A DNA segment of the present invention can easily be prepared from isolated virus obtained from the blood of a NANBV-infected individual such as described herein or can be synthesized by chemical techniques, for example, the phosphotriester method of Matteucci et al., J. Am. Chem. Soc., 103:3185 (1981). (The disclosures of the art cited herein are incorporated herein by reference.) Of course, by chemically synthesizing the structural gene portion, any desired modifications can be made simply by substituting the appropriate bases for those encoding a native amino acid residue. However, DNA segments including sequences identical to a segment contained in SEQ. ID NOS. 1, 2, (3, 4 or 6) are preferred.

20 In addition, a DNA segment can be prepared by first synthesizing oligonucleonucleotides that correspond to portions of the DNA segment, which oligonucleotides are then assembled by hybridization and ligation into a complete DNA segment. Such methods are also well known in the art. See for example, Paterson et al., Cell, 48:441-452 (1987); and Lindley

et al., Proc.Natl. Acad. Sci., 85:9199-9203 (1988), where a recombinant peptide, neutrophil-activated factor, was produced from the expression of a chemically synthesized gene in E. coli.

5 C. Recombinant DNA Molecules

The present invention further contemplates a recombinant DNA (rDNA) that includes a DNA segment of the present invention operatively linked to a vector. A preferred rDNA of the present invention is
10 characterized as being capable of directly expressing, in a compatible host, a NANBV structural protein or fusion protein of this invention. Preferred DNA
* segments for use in a rDNA are those described herein above.

15 By "directly expressing" is meant that the mature polypeptide chain of the protein is formed by translation alone as opposed to proteolytic cleavage of two or more terminal amino acid residues from a larger translated precursor protein. Preferred rDNAs
20 of the present invention are the plasmids pGEX-3X-690:694, pGEX-3X-693:691, pGEX-3X-690:691, pGEX-3X-15:17, pGEX-3X-15:18, pGEX-2T-15:17, pGEX-2T-CAP-A, pGEX-2T-CAP-B, and pGEX-2T-CAP-A-B described in Example 1.

25 A recombinant DNA molecule of the present invention can be produced by operatively linking a vector to a DNA segment of the present invention. Exemplary rDNA molecules and the methods for their preparation are described in Example 1.

30 As used herein, the term "vector" refers to a DNA molecule capable of autonomous replication in a cell and to which another DNA segment can be operatively linked so as to bring about replication of the attached segment. Typical vectors are plasmids,
35 bacteriophage and the like. Vectors capable of directing the expression of a NANBV structural protein

or fusion protein are referred to herein as "expression vectors". Thus, a recombinant DNA molecule (rDNA) is a hybrid DNA molecule comprising at least two nucleotide sequences not normally found together in nature.

The choice of vector to which a DNA segment of the present invention is operatively linked depends directly, as is well known in the art, on the functional properties desired, e.g., protein expression, and the host cell to be transformed, these being limitations inherent in the art of constructing recombinant DNA molecules. However, a vector contemplated by the present invention is at least capable of directing the replication, and preferably also expression, of the recombinant or fusion protein structural gene included in DNA segments to which it is operatively linked.

In preferred embodiments, a vector contemplated by the present invention includes a procaryotic replicon (ori), i.e., a DNA sequence having the ability to direct autonomous replication and maintenance of the recombinant DNA molecule extrachromosomally in a procaryotic host cell, such as a bacterial host cell, transformed therewith. Such replicons are well known in the art. In addition, those embodiments that include a procaryotic replicon also typically include a gene whose expression confers drug resistance to a bacterial host transformed therewith. Typical bacterial drug resistance genes for use in these vectors are those that confer resistance to ampicillin or tetracycline. Typical of such vector plasmids are pUC8, pUC9, pBR322 and pBR329 available from Biorad Laboratories, (Richmond, CA).

Those vectors that include a procaryotic replicon can also include a procaryotic promoter capable of directing the expression (transcription and

translation) of the gene encoding a NANBV structural protein or fusion protein in a bacterial host cell, such as E. coli, transformed therewith. A promoter is an expression control element formed by a DNA sequence that permits binding of RNA polymerase and transcription to occur. Promoter sequences compatible with bacterial hosts are typically provided in plasmid vectors containing convenient restriction sites for insertion of a DNA segment of the present invention. A typical vector is pPL-lambda available from Pharmacia, (Piscataway, NJ).

Vector plasmids having a bacterial promoter that is inducible with IPTG are the pTTQ plasmids available from Amersham (Arlington Heights, IL), and the pKK223-3 plasmid available from Pharmacia. Additional expression vectors for producing in procaryotes a cloned gene product in the form of a fusion protein are well known and commercially available.

Although the expression vectors pGEX-3X and pGEX-2T have been used as exemplary in producing the fusion proteins described herein, other functionally equivalent expression vectors can be used. Functionally equivalent vectors contain an expression promoter that is inducible by IPTG for fusion protein expression in E. coli, and a configuration such that upon insertion of the DNA segment into the vector a fusion protein is produced. Commercially available vector^S functionally equivalent to the vectors pGEX-3X and pGEX-2T used herein include the pGEMEX-1 plasmid vector from Promega (Madison, WI) that produces a fusion between the amino terminal portion of the T7 gene 10 protein and the cloned insert gene, and the pGEX-3X and pGEX-2T plasmids from Pharmacia that produce a fusion with the enzyme glutathione-s-transferase (GST).

The construction and use of the pGEX-3X and pGEX-2T vectors have been described by Smith et al., Gene, 67:31-40 (1988), which reference is hereby incorporated by reference.

5 In particularly preferred embodiments, a fusion protein contains a GST derived polypeptide-portion as an added functional domain operatively linked to a NANBV structural antigen of this invention. Any inducible promoter driven vector, such as the vectors
10 pTTQ, pKK223-3, pGEX-3X or pGEX-2T described above and the like, can be used to express a GST-NANBV structural protein, referred to herein as a GST:NANBV fusion protein. Thus, although the pGEX-3X and pGEX-2T vectors are described as exemplary, the DNA
15 molecules of this invention are not to be construed as limited to these vectors, because the invention in one embodiment is directed to an rDNA for expression of a protein having NANBV structural antigens fused to GST and not drawn to the vector per se.

20 A variety of methods have been developed to operatively link DNA segments to vectors via complementary cohesive termini. For instance, complementary homopolymer tracts can be added to the DNA segment to be inserted and to the vector DNA. The
25 vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric tails to form recombinant DNA molecules.

Synthetic linkers containing one or more restriction sites provide an alternative method of
30 joining the DNA segment to vectors. A DNA segment generated by endonuclease restriction digestion is treated with bacteriophage T4 DNA polymerase or E. coli DNA polymerase I, enzymes that remove protruding, 3', single-stranded termini with their 3'-5' exonucleolytic activities and fill in recessed 3' ends
35 with their polymerizing activities. The combination

of these activities therefore generates blunt-ended DNA segments. The blunt-ended segments are then incubated with a large molar excess of linker molecules in the presence of an enzyme that is able to catalyze the ligation of blunt-ended DNA molecules, such as bacteriophage T4 DNA ligase. Thus, the products of the reaction are DNA segments carrying polymeric linker sequences at their ends. These DNA segments are then cleaved with the appropriate restriction enzyme and ligated to an expression vector that has been cleaved with an enzyme that produces termini compatible with those of the DNA segment.

Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies, Inc., New Haven, CN.

Also contemplated by the present invention are RNA equivalents of the above described recombinant DNA molecules.

D. Transformed Cells and Cultures

The present invention also relates to a procaryotic host cell transformed with a recombinant DNA molecule of the present invention. Preferred rDNA molecules for use in a transformed cell are those described herein above and preferably are rDNA's capable of expressing a recombinant or fusion protein. Specific preferred embodiments of transformed cells are those which contain an rDNA molecule having one of the preferred DNA segments described herein above, and particularly cells transformed with the rDNA plasmid pGEX-3X-690:694, pGEX-3X-693:691, pGEX-3X-690:691, pGEX-3X-15:17, pGEX-3X-15:18, pGEX-2T-15:17, (pGEX-2T-CAP-A, pGEX-2T-CAP-B, or pGEX-2T-CAP-A-B.)

Bacterial cells are preferred procaryotic host cells and typically are a strain of E. coli, such as, for example, the E. coli strain DH5 available from

Bethesda Research Laboratories, Inc., Bethesda, MD. Transformation of appropriate cell hosts with a recombinant DNA molecule of the present invention is accomplished by well known methods that typically depend on the type of vector used. With regard to transformation of procaryotic host cells, see, for example, Cohen et al., Proc. Natl. Acad. Sci. USA, 69:2110 (1972); and Maniatis et al., Molecular Cloning, A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989).

Successfully transformed cells, i.e., cells that contain a recombinant DNA molecule of the present invention, can be identified by well known techniques. For example, cells resulting from the introduction of an rDNA of the present invention can be isolated as single colonies. Cells from those colonies can be harvested, lysed and their DNA content examined for the presence of the rDNA using a method such as that described by Southern, J. Mol. Biol., 98:503 (1975) or Berent et al., Biotech., 3:208 (1985).

In addition to directly assaying for the presence of rDNA, cells transformed with the appropriate rDNA can be identified by well known immunological methods when the rDNA is capable of directing the expression of a NANBV structural protein. For example, cells successfully transformed with an expression vector of this invention produce proteins displaying NANBV structural protein antigenicity. Samples of cells suspected of being transformed are harvested and assayed for the presence of a NANBV structural antigen using antibodies specific for that antigen, such antibodies being described further herein.

Thus, in addition to the transformed host cells themselves, the present invention also contemplates a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived

from a monoclonal culture, in a nutrient medium. Preferably, the culture also contains a protein displaying NANBV structural protein antigenicity.

5 Nutrient media useful for culturing transformed host cells are well known in the art and can be obtained from several commercial sources.

E. Methods for Producing NANBV structural proteins and Fusion Proteins

10 Another aspect of the present invention pertains to a method for producing recombinant proteins and fusion proteins of this invention.

The present method entails initiating a culture comprising a nutrient medium containing host cells, preferably E. coli cells, transformed with a
15 recombinant DNA molecule of the present invention that is capable of expressing a NANBV structural protein or a fusion protein. The culture is maintained for a time period sufficient for the transformed cells to express the NANBV structural protein or fusion
20 protein. The expressed protein is then recovered from the culture.

Expression vectors and expression vector culturing conditions for producing NANBV structural proteins are generally well known in the art. Such
25 vectors and culturing conditions can be altered without affecting the spirit of the present invention. However, preferred are the vectors designed specifically for the production of proteins not normally found in the host cell used to express a
30 NANBV structural protein. Exemplary are the vectors that contain inducible promoters for directing the expression of DNA segments that encode the NANBV structural protein. Vectors with promoters inducible by IPTG are also well known. See for example plasmids
35 pTTQ and pKK223-3 available from Amersham and Pharmacia respectively. Particularly preferred are

the promoters inducible by IPTG present in the pGEX vectors pGEX-3X and pGEX-2T described herein.

Using vectors with inducible promoters, expression of NANBV structural proteins requires an induction phase at the beginning of the above described maintenance step for expressing the protein, as is known and described in detail in Example 2.

Methods for recovering an expressed protein from a culture are well known in the art and include fractionation of the protein-containing portion of the culture using well known biochemical techniques. For instance, the methods of gel filtration, gel chromatography, ultrafiltration, electrophoresis, ion exchange, affinity chromatography and the like, such as are known for protein fractionations, can be used to isolate the expressed proteins found in the culture. In addition, immunochemical methods, such as immunoaffinity, immunoadsorption and the like can be performed using well known methods.

Particularly preferred are isolation methods that utilize the presence of the polypeptide portion defining glutathione-S-transferase (GST) as a means to separate the fusion protein from complex mixtures of protein. Affinity adsorption of a GST-containing fusion protein to a solid phase containing glutathione affixed thereto can be accomplished as described by Smith et al., Gene, 67:31 (1988). Alternatively, the GST-containing polypeptide portion of the fusion protein can be separated from the NANBV structural antigen by selective cleavage of the fusion protein at the factor Xa cleavage site, according to the methods of Smith et al., Gene, 67:31 (1988). Exemplary isolation methods are described in Examples 5 and 6.

In addition to its preparation by the use of a rDNA expression vector, a NANBV structural protein comprising a NANBV structural antigen can be prepared

in the form of a synthetic polypeptide. Polypeptides can be synthesized by any of the techniques that are known to those skilled in the polypeptide art.

Synthetic chemistry techniques, such as a solid-phase Merrifield-type synthesis, are preferred for reasons of purity, antigenic specificity, freedom from undesired side products, ease of production and the like, and can be carried out according to the methods described in Merrifield et al., J. Am. Chem. Soc., 85:2149-2154 (1963) and Houghten et al., Int. J. Pept. Prot. Res., 16:311-320 (1980). An excellent summary of the many techniques available can be found in J.M. Steward and J.D. Young, "Solid Phase Peptide Synthesis", W.H. Freeman Co., San Francisco, 1969; M. Bodanszky, et al., "Peptide Synthesis", John Wiley & Sons, Second Edition, 1976, and J. Meienhofer, "Hormonal Proteins and Peptides", Vol. 2, p. 46, Academic Press (NY), 1983, for solid phase peptide synthesis, and E. Schroder and K. Kubke, "The Peptides", Vol. 1, Academic Press (New York), 1965, for classical solution synthesis, each of which is incorporated herein by reference.

F. NANBV structural protein and Fusion Protein Compositions

In another embodiment, the present invention contemplates a composition containing an isolated NANBV structural protein comprising an amino acid residue sequence that defines a NANBV structural antigen of this invention.

By isolated is meant that a NANBV structural protein of this invention is present in a composition as a major protein constituent, typically in amounts greater than 10% of the total protein in the composition, but preferably is greater than 90% of the total protein in the composition.

A NANBV structural antigen, as used herein, is a structural protein coded by the genome of NANBV and has the properties of an antigen as defined herein, namely, to be able to immunoreact specifically with an antibody. NANBV structural proteins have been tentatively designated as capsid and envelope, and have been partially characterized as described herein to contain the NANBV structural antigens capsid and envelope, respectively.

NANBV capsid antigen comprises an amino acid residue sequence that is immunologically related in sequence to the putative Hutch strain NANBV capsid antigen, whose sequence is contained in SEQ. ID NO. 1 from residue 1 to residue 120.

NANBV envelope antigen comprises an amino acid residue sequence that is immunologically related in sequence to the putative Hutch strain NANBV envelope antigen, a portion of whose sequence is contained in SEQ. ID NO. 1 from residue 121 to residue 326.

By "immunologically related" is meant that sufficient homology in amino acid sequence is present in the two protein sequences being compared that antibodies specific for one protein immunoreact (crossreact) with the other protein. Immunological crossreactivity can be measured by methods well known including the immunoassay methods described herein.

As used herein, the phrase "recombinant protein" refers to a protein of at least 20 amino acid residues in length, and preferably at least 50 residues, that includes an amino acid residue sequence that corresponds, and preferably is identical, to a portion of the NANBV structural protein contained in SEQ. ID NO. 1.

In preferred embodiments a NANBV structural protein includes an amino acid residue sequence that is immunologically related to, and preferably is

identical to, the sequence contained in SEQ. ID NO. 1 from (residue 1 to residue 20, from residue 21 to residue 40, from residue 2 to residue 40), or from residue 1 to residue 74. The NANBV structural protein
5 with the indicated sequence is particularly preferred for use in diagnostic methods and systems because the capsid antigens contained therein were demonstrated herein to be particularly useful in detecting acute NANBV infection. Related NANBV structural proteins
10 include a sequence contained in SEQ. ID NO. 1 from residue 1 to residue 120, from residue 1 to residue 176, and from residue 1 to residue 326. Exemplary are the proteins described herein having a sequence contained in SEQ. ID NO. 2 from residue 1 to residue
15 315, (in SEQ. ID NO. 3 from residue 1 to residue 252, in SEQ. ID NO. 4 from residue 1 to residue 252, or in SEQ. ID NO. 6 from residue 1 to residue 271.

In another embodiment a NANBV structural protein includes an amino acid residue sequence that is
20 immunologically related to, and preferably is identical to, the sequence contained in SEQ. ID NO. 1 from residue 69 to residue 120. An exemplary NANBV structural protein has the sequence of the expressed protein coded for by the rDNA plasmid pGEX-3X-693:691.

25 Additional NANBV structural proteins containing NANBV envelope antigen are contemplated that include an amino acid residue sequence that is immunologically related to, and preferably is identical to, the sequence contained in SEQ. ID NO. 1 from residue 121
30 to residue 176. Exemplary are the proteins having a sequence of the expressed protein coded for by one of the rDNA plasmids pGEX-3X-15:17, pGEX-3X-15:18 and pGEX-2T-15:17.

In preferred embodiments a NANBV structural
35 protein is essentially free of both procaryotic antigens (i.e., host cell-specific antigens) and other

NANBV-related proteins. By "essentially free" is meant that the ratio of NANBV structural antigen to either procaryotic antigen or other NANBV-related protein is at least 10:1, preferably is 100:1, and more preferably is 200:1.

The presence and amount of contaminating protein in a NANBV structural protein preparation can be determined by well known methods. Preferably, a sample of the composition is subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) to separate the NANBV structural protein from any protein contaminants present. The ratio of the amounts of the proteins present in the sample is then determined by densitometric soft laser scanning, as is well known in the art. See Guilian et al., Anal. Biochem., 129:277-287 (1983).

A NANBV structural protein can be prepared as an isolated protein, and more preferably essentially free of procaryotic antigens or NANBV non-structural antigens by the methods disclosed herein for producing NANBV structural proteins. Particularly preferred are methods which rely on the properties of a polypeptide region of a fusion protein, which region is present in the fusion protein to facilitate separation of the fusion protein from host cell proteins on the basis of affinity. Exemplary are the GST-containing fusion proteins contained in SEQ. ID NOS. 2, 3, 4 or 6 wherein the GST polypeptide region of each provides the fusion protein with a functional domain having an affinity to bind to the normal substrate for GST, namely glutathione. The purification of a fusion protein having a GST polypeptide region is described further herein.

In a related embodiment, a composition comprising an isolated fusion protein is also contemplated by the present invention that comprises a NANBV structural

protein of this invention operatively linked at one or both termini to another polypeptide by a peptide bond. The added polypeptide can be any polypeptide designed to increase the functional domains present on the fusion protein. The added functional domains are included to provide additional immunogenic epitopes, to add mass to the fusion protein, to alter the solubility of the fusion protein, to provide a means for affinity-based isolation of the fusion protein, and the like. Exemplary added functional domains are the Thrombin or Factor Xa specific cleavage sites provided when a subject fusion protein is produced in the vector pGEX-3X or pGEX-2T, respectively, as described herein. An additional exemplary domain is the GST-derived protein domain that allows rapid isolation using affinity chromatography to a solid phase containing glutathione affixed thereto.

new < A Thrombin or Factor Xa cleavage site-containing domain is used herein, in one embodiment, to allow production of an NANBV structural protein free of the GST function domain. Exemplary is the protein produced in Example 6 having an amino acid residue sequence contained in SEQ. ID NO. 2 from residue 226 to residue 315. In a related embodiment a NANBV structural protein is produced by Thrombin cleavage of a protein produced using the pGEX-2T vector, such as a protein having an amino acid residue sequence contained in SEQ. ID NO. 3 from residue 225 to residue 252, in SEQ. ID NO. 4 from residue 225 to residue 252, or in SEQ. ID NO. 6 from residue 225 to residue 271.

A fusion protein of the present invention includes an amino acid residue sequence corresponding from its amino-terminus to its carboxy-terminus to the amino acid residue sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20, from residue 21 to residue 40, from residue 2 to residue 40,) from residue

1 to residue 74, from residue 69 to residue 120, from
residue 121 to residue 176, or from residue 121 to
residue 326. A preferred fusion protein has a
sequence corresponding to, and more preferably is
5 identical to, the amino acid residue sequence in SEQ.
ID NO. 2 from residue 1 to residue 315, (in SEQ. ID NO.
3 from residue 1 to residue 252, in SEQ. ID NO. 4 from
residue 1 to residue 252, or in SEQ. ID NO. 6 from
residue 1 to residue 271.) Other preferred fusion
10 proteins are defined by the amino acid residue
sequence of the expressed protein coding sequence
present in the rDNA plasmids pGEX-3X-690:694, pGEX-3X-
690:691, pGEX-3X-693:691, pGEX-3X-15:17, pGEX-3X-
15:18, pGEX-2T-15:17, (pGEX-2T-CAP-A, pGEX-2T-CAP-B,
15 and pGEX-2T-CAP-A-B.)

The phrase "fusion protein", when used herein
refers to an isolated protein as it was defined for a
NANBV structural protein of this invention. Thus an
isolated fusion protein is a composition having a
20 fusion protein of this invention in amounts greater
than 10 percent of the total protein in the
composition, and preferably greater than 90 percent of
the total protein in the composition.

A preferred fusion protein is a heterologous
25 fusion protein, that is, a fusion protein that
contains a polypeptide portion derived from a protein
originating in a heterologous species of virus,
organism, pathogen or animal, i.e., a non-NANBV
protein. Preferably a heterologous fusion protein
30 contains a non-NANBV polypeptide portion that is not
immunologically related to a NANBV structural antigen
of this invention.

In one embodiment, a fusion protein contains a
functional domain that provides an immunogenic or
35 antigenic epitope other than the NANBV structural
antigen defined herein and is preferably derived from

a separate pathogen, or from several pathogens. The functional domain is immunogenic where that domain is present to form a polyvalent vaccine or immunogen for the purpose of inducing antibodies immunoreactive with both NANBV structural protein and a second pathogen. The functional domain is antigenic where that domain is present to form a polyvalent antigen for use in diagnostic systems and methods for detecting at least two species of antibodies.

Of particular interest in this embodiment are fusion proteins designed to include a functional domain that is derived from other hepatitis-causing viruses, such as Hepatitis B virus, and Hepatitis A virus. These viruses have been well characterized to contain antigenic determinants and immunogenic determinants suitable for use in the fusion protein of this invention, and provide the advantage of multipurpose biochemical reagents in both diagnostic and vaccine applications. Additionally, the included functional domain can contain amino acid sequences from other pathogens, preferably those which may also infect individuals with NANBV hepatitis, such as HIV.

Preferred NANBV structural proteins or fusion proteins comprising a NANBV structural antigen of the present invention are in non-reduced form, i.e., are substantially free of sulfhydryl groups because of intramolecular Cys-Cys bonding.

In preferred compositions, the NANBV structural protein or fusion protein as described herein, is present, for example, in liquid compositions such as sterile suspensions or solutions, or as isotonic preparations containing suitable preservatives.

One such composition useful for inducing anti-NANBV structural protein antibodies in a mammal is referred to as a vaccine and contains a NANBV

structural protein or fusion protein of this invention.

G. Vaccines

1. Introduction

5 The word "vaccine" in its various grammatical forms is used herein to describe a type of inoculum containing one or more NANBV structural antigens of this invention as an active ingredient in a pharmaceutically acceptable excipient that is used to induce active immunity in a host mammal against NANBV.

10 A vaccine comprises, as an active immunogenic ingredient, a NANBV structural protein or fusion protein of this invention.

15 Because a vaccine is typically designed to induce specific antibodies, it is preferred that a vaccine contain a NANBV structural protein comprised of only NANBV structural antigens and not other functional domains as described for a fusion protein. Thus a preferred vaccine contains a NANBV structural protein of this invention that includes an amino acid residue sequence contained in SEQ. ID NO. 1 (from residue 1 to residue 20, from residue 21 to residue 40, from residue 2 to residue 40, from residue 1 to residue 74, from residue 69 to residue 120, from residue 121 to residue 176, or from residue 121 to residue 326. Particularly preferred as an active ingredient in a vaccine is a NANBV structural protein having the amino acid residue sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20, from residue 21 to residue 40, from residue 2 to residue 40, from residue 1 to residue 74, from residue 1 to residue 120, or contained in SEQ. ID NO. 2 from residue 226 to residue 315, contained in SEQ. ID NO. 3 from residue 225 to residue 252, contained in SEQ. ID NO. 4 from residue 225 to residue 252, or contained in SEQ. ID NO. 6 from residue 225 to residue 271.)

Alternatively, a polyvalent vaccine is contemplated that comprises a fusion protein that has two immunogenic functional domains and is useful to induce two classes of antibodies each specific for a different antigen; namely a first NANBV structural antigen as described herein, and a second antigen present on a distinct pathogen. Preferred second antigens are derived from pathogens that are typically found in association with NANBV-infected patients, namely Hepatitis B Virus, Human Immunodeficiency Virus (HIV) and the like.

2. Preparation

The preparation of a vaccine that contains a protein or polypeptide as an active ingredient is well understood in the art. Typically, such vaccines are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. The preparation can also be emulsified.

The active immunogenic ingredient is dissolved, dispersed or admixed in an excipient that is pharmaceutically acceptable and compatible with the active ingredient as is well known. The phrases "suitable for human use" and "pharmaceutically acceptable" (physiologically tolerable) refer to molecular entities and compositions that typically do not produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. Suitable excipients may take a wide variety of forms depending on the intended use and are, for example, aqueous solutions containing saline, phosphate buffered saline (PBS), dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the vaccine can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents,

mineral oils, carriers or adjuvants which enhance the effectiveness of the vaccine. A preferred embodiment contains at least about 0.01% to about 99% of NANBV structural protein or fusion as an active ingredient, typically at a concentration of about 10 to 200 ug of active ingredient per ml of excipient.

3. Carriers

One or more additional amino acid residues may be added to the amino- or carboxy-termini of the NANBV structural protein to assist in binding the protein to a carrier if not already present on the protein. Cysteine residues added at the amino- or carboxy-termini of the protein have been found to be particularly useful for forming polymers via disulfide bonds. However, other methods well known in the art for preparing conjugates can also be used. Exemplary additional linking procedures include the use of Michael addition reaction products, dialdehydes such as glutaraldehyde, Klipstein et al., J. Infect. Dis., 147:318-326 (1983) and the like, or the use of carbodiimide technology as in the use of a water-soluble carbodiimide to form amide links to the carrier.

Useful carriers are well known in the art, and are generally proteins themselves. Exemplary of such carriers are keyhole limpet hemocyanin (KLH), edestin, thyroglobulin, albumins such as bovine serum albumin (BSA) or human serum albumin (HSA), red blood cells such as sheep erythrocytes (SRBC), tetanus toxoid, cholera toxoid as well as poly amino acids such as poly (D-lysine: D-glutamic acid), and the like.

As is also well known in the art, it is often beneficial to bind a NANBV structural protein to its carrier by means of an intermediate, linking group. As noted above, glutaraldehyde is one such linking group. However, when cysteine is used, the

intermediate linking group is preferably an m -maleimidobenzoyl N-hydroxy succinimide (MBS).

Additionally, MBS may be first added to the carrier by an ester-amide interchange reaction.

5 Thereafter, the addition can be followed by addition of a blocked mercapto group such as thiolacetic acid (CH_3COSH) across the maleimido-double bond. After cleavage of the acyl blocking group, a disulfide bond is formed between the deblocked linking group
10 mercaptan and the mercaptan of the cysteine residue of the protein.

Other means of immunopotential include the use of liposomes and immuno-stimulating complex (ISCOM) particles. The unique versatility of liposomes lies
15 in their size adjustability, surface characteristics, lipid composition and ways in which they can accommodate antigens. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Vol. XIV, Academic Press, NY
20 (1976) p.33 et seq. In ISCOM particles, the cage-like matrix is composed of Quil A, extracted from the bark of a South American tree. A strong immune response is evoked by antigenic proteins or peptides attached by hydrophobic interaction with the matrix surface.

25 The choice of carrier is more dependent upon the ultimate use of the immunogen than upon the determinant portion of the immunogen, and is based upon criteria not particularly involved in the present invention. For example, if an inoculum is to be used
30 in animals, a carrier that does not generate an untoward reaction in the particular animal should be selected.

4. Administration

35 The vaccines are conventionally administered parenterally, by injection, for example, either subcutaneously or intramuscularly. Additional

formulations which are suitable for other modes of administration include suppositories and, in some cases, oral formulations. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1-2%. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. The compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10%-95% of active ingredient, preferably 25-70%.

A NANBV structural protein can be formulated into a vaccine as a neutral or salt form. Pharmaceutically acceptable salts, include the acid addition salts (formed with the free amino groups of the antigen) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine, and the like.

The vaccines are administered in a manner compatible with the dosage formulation, and in such amount as will be immunogenic and effective to induce an immune response. The quantity to be administered to achieve desired full protective immunity depends on the subject to be immunized, capacity of the subject's immune system to synthesize antibodies or induce cell-

mediated response, and the degree of protection desired. Precise amounts of active ingredient required to be administered depend on the judgement of the practitioner and are peculiar to each individual, but generally a dosage suitable for a broad population can be defined. Suitable dosage ranges are of the order of about ten micrograms (ug) to several milligrams (mg), preferably about 10-500 micrograms and more preferably about 100 micrograms active ingredient for each single immunization dose for a human adult. Suitable regimes for initial administration and booster shots are also variable, but are typified by an initial administration followed in two to six week intervals by a subsequent injection or other administration.

A vaccine can also include an adjuvant as part of the excipient. Adjuvants such as complete Freund's adjuvant (CFA), incomplete Freund's adjuvant (IFA) for use in laboratory mammals are well known in the art. Pharmaceutically acceptable adjuvants such as alum can also be used. An exemplary vaccine thus comprises one ml of phosphate buffered saline (PBS) containing about 50 to 200 ug NANBV structural protein adsorbed onto about 0.5 mg to about 2.5 mg of alum, or to 0.1% to 1% Al(OH)₃. A preferred vaccine comprises 1 ml of PBS containing 100 ug NANBV structural protein adsorbed onto 2.5 mg of alum carrier.

H. Antibody Compositions

An antibody of the present invention is a composition containing antibody molecules that immunoreact with a NANBV structural antigen and with a NANBV structural protein of the present invention (anti-NANBV structural protein antibody molecules). A preferred antibody contains antibody molecules that immunoreact with an epitope present on a polypeptide having an amino acid residue sequence contained in

SEQ. ID NO. 1 from residue 1 to residue 326,
preferably that immunoreacts with a polypeptide having
the sequence contained in SEQ. ID NO. 1 (from residue 1
to residue 20, from residue 21 to residue 40, from
5 residue 2 to residue 40, from residue 1 to residue 74,
from residue 49 to residue 120, or from residue 121 to
residue 326.

In addition, it is preferred that anti-NANBV
structural protein antibody molecules do not
10 immunoreact with the C-100-3 antigen described herein,
and available in the commercial assay available from
Ortho Diagnostics, Inc.

An antibody of the present invention is typically
produced by immunizing a mammal with an inoculum
15 containing a NANBV structural protein of this
invention and thereby induce in the mammal antibody
molecules having immunospecificity for the NANBV
structural antigens described herein. The antibody
molecules are then collected from the mammal and
20 isolated to the extent desired by well known
techniques such as, for example, by using DEAE
Sephadex to obtain the IgG fraction.

To enhance the specificity of the antibody, the
antibodies may be purified by immunoaffinity
25 chromatography using solid phase-affixed immunizing
NANBV structural protein. The antibody is contacted
with the solid phase-affixed NANBV structural protein
for a period of time sufficient for the NANBV
structural protein to immunoreact with the antibody
30 molecules to form a solid phase-affixed immunocomplex.
The bound antibodies are separated from the complex by
standard techniques.

The antibody so produced can be used, inter alia,
in the diagnostic methods and systems of the present
35 invention to detect NANBV structural antigens as
described herein present in a body sample.

The word "inoculum" in its various grammatical forms is used herein to describe a composition containing a NANBV structural antigen of this invention as an active ingredient used for the preparation of antibodies immunoreactive with NANBV structural antigens.

The preparation and use of an inoculum for production of an antibody of this invention largely parallels the descriptions herein for a vaccine insofar as the vaccine is also designed to induce the production of antibodies and is exemplary of the preparation and use of an inoculum. A key difference is that the inoculum is formulated for use on an animal rather than a human, as is well known.

A preferred antibody is a monoclonal antibody and can be used in the same manner as disclosed herein for antibodies of the present invention.

A monoclonal antibody is typically composed of antibodies produced by clones of a single cell called a hybridoma that secretes (produces) but one kind of antibody molecule. The hybridoma cell is formed by fusing an antibody-producing cell and a myeloma or other self-perpetuating cell line. The preparation of such antibodies were first described by Kohler and Milstein, Nature 256:495-497 (1975), which description is incorporated by reference. The hybridoma supernates so prepared can be screened for immunoreactivity with a NANBV structural antigen such as the NANBV structural protein used in the inoculum to induce the antibody-producing cell. Other methods of producing monoclonal antibodies, the hybridoma cell, and hybridoma cell cultures are also well known.

Also contemplated by this invention is the hybridoma cell, and cultures containing a hybridoma cell that produce a monoclonal antibody of this invention.

It should be understood that in addition to the
aforementioned carrier ingredients the pharmaceutical
formulation described herein can include, as
appropriate, one or more additional carrier
5 ingredients such as diluents, buffers, binders,
surface active agents, thickness, lubricants,
preservatives (including antioxidants) and the like,
and substances included for the purpose of rendering
the formulation isotonic with the blood of the
10 intended recipient. Typically, a preservative such as
merthiolate (at a 1:5000 dilution of a 1% solution) is
added to eliminate the risk of microbial
contamination, even if sterile techniques were
employed in the manufacture of the vaccine.

15 I. Diagnostic Systems and Methods

1. Diagnostic Systems

A diagnostic system in kit form includes, in an
amount sufficient for at least one assay according to
the methods described herein, a NANBV structural
20 protein or a fusion protein of the present invention,
as a separately packaged reagent. Instructions for
use of the packaged reagent are also typically
included.

"Instructions for use" typically include a
25 tangible expression describing the reagent
concentration or at least one assay method parameter
such as the relative amounts of reagent and sample to
be admixed, maintenance time periods for
reagent/sample admixtures, temperature, buffer
30 conditions and the like.

In preferred embodiments, a diagnostic system of
the present invention further includes a label or
indicating means capable of signaling the formation of
a complex containing a recombinant protein.

35 As used herein, the terms "label" and "indicating
means" in their various grammatical forms refer to

single atoms and molecules that are either directly or indirectly involved in the production of a detectable signal to indicate the presence of a complex. Any label or indicating means can be linked to or
5 incorporated in an antibody or monoclonal antibody or used separately, and those atoms or molecules can be used alone or in conjunction with additional reagents. Such labels are themselves well-known in clinical diagnostic chemistry and constitute a part of this
10 invention only insofar as they are utilized with otherwise novel proteins, methods and/or systems.

The label can be a fluorescent labeling agent that chemically binds to antibodies or antigens without denaturing them to form a fluorochrome (dye)
15 that is a useful immunofluorescent tracer. Suitable fluorescent labeling agents are fluorochromes such as fluorescein isocyanate (FIC), fluorescein isothiocyanate (FITC), 5-dimethylamine-1-naphthalenesulfonyl chloride (DANSC),
20 tetramethylrhodamine isothiocyanate (TRITC), lissamine, rhodamine 8200 sulphonyl chloride (RB 200 SC), a chelate-lanthanide bound (e.g., Eu, Tb, Sm) and the like. A description of immunofluorescence analysis techniques is found in DeLuca,
25 "Immunofluorescence Analysis", in Antibody As a Tool, Marchalonis, et al., eds., John Wiley & Sons, Ltd., pp. 189-231 (1982), which is incorporated herein by reference.

In preferred embodiments, the label is an enzyme,
30 such as horseradish peroxidase (HRP), glucose oxidase, alkaline phosphatase or the like. In such cases where the principal label is an enzyme such as HRP or glucose oxidase, additional reagents are required to visualize the fact that an antibody-antigen complex
35 (immunoreactant) has formed. Such additional reagents for HRP include hydrogen peroxide and an oxidation dye

precursor such as diaminobenzidine. An additional reagent useful with HRP is 2,2'-azino-di-(3-ethyl-benzthiazoline-6-sulfonic acid) (ABTS).

Radioactive elements are also useful labeling agents and are used illustratively herein. An exemplary radiolabeling agent is a radioactive element that produces gamma ray emissions. Elements which themselves emit gamma rays, such as ^{124}I , ^{125}I , ^{128}I , ^{131}I and ^{51}Cr represent one class of gamma ray emission-producing radioactive element indicating groups. Particularly preferred is ^{125}I . Another group of useful labeling means are those elements such as ^{11}C , ^{18}F , ^{15}O , and ^{13}N which themselves emit positrons. The positrons so emitted produce gamma rays upon encounters with electrons present in the animal's body. Also useful is a beta emitter, such as ^{111}In , indium, ^3H , ^{35}S , ^{14}C , or ^{32}P .

Additional labels have been described in the art and are suitable for use in the diagnostic systems of this invention. For example, the specific affinity found between pairs of molecules can be used, one as a label affixed to the specific binding agent and the other as a means to detect the presence of the label. Exemplary pairs are biotin:avidin, where biotin is the label, and peroxidase:anti-peroxidase (PAP), where peroxidase is the label.

The linking of labels, i.e., labeling of, polypeptides and proteins is well known in the art. For instance, antibody molecules produced by a hybridoma can be labeled by metabolic incorporation of radioisotope-containing amino acids provided as a component in the culture medium. See, for example, Galfre et al., Meth. Enzymol., 73:3-46 (1981). The techniques of protein conjugation or coupling through activated functional groups are particularly applicable. See, for example, Aurameas, et al.,

Scand. J. Immunol., Vol. 8 Suppl. 7:7-23 (1978), Rodwell et al., Biotech., 3:889-894 (1984), and U.S. Pat. No. 4,493,795.

5 The diagnostic systems can also include, preferably as a separate package, a specific binding agent. A "specific binding agent" is a molecular entity capable of selectively binding a reagent species, which in turn is capable of reacting with a product of the present invention but is not itself a
10 protein expression product of the present invention. Exemplary specific binding agents are antibody molecules such as anti-human IgG or anti-human IgM, complement proteins or fragments thereof, protein A, and the like. Preferably the specific binding agent
15 can bind the anti-NANBV antibody to be detected when the antibody is present as part of an immunocomplex.

In preferred embodiments the specific binding agent is labeled. However, when the diagnostic system includes a specific binding agent that is not labeled,
20 the agent is typically used as an amplifying means or reagent. In these embodiments, the labeled specific binding agent is capable of specifically binding the amplifying means when the amplifying means is bound to a reagent species-containing complex.

25 The diagnostic kits of the present invention can be used in an "ELISA" format to detect the presence or quantity of antibodies in a body fluid sample such as serum, plasma or saliva. "ELISA" refers to an enzyme-linked immunosorbent assay that employs an antibody or
30 antigen bound to a solid phase and an enzyme-antigen or enzyme-antibody conjugate to detect and quantify the amount of an antigen or antibody present in a sample. A description of the ELISA technique is found in Chapter 22 of the 4th Edition of Basic and Clinical
35 Immunology by D.P. Sites et al., published by Lange Medical Publications of Los Altos, CA in 1982 and in

U.S. Patents No. 3,654,090; No. 3,850,752; and No. 4,016,043, which are all incorporated herein by reference.

Thus, in preferred embodiments, the NANBV structural protein or fusion protein of the present invention can be affixed to a solid matrix to form a solid support that is separately packaged in the subject diagnostic systems.

The reagent is typically affixed to the solid matrix by adsorption from an aqueous medium although other modes of affixation, well known to those skilled in the art, can be used.

Useful solid matrices are well known in the art. Such materials include the cross-linked dextran available under the trademark SEPHADEX from Pharmacia Fine Chemicals (Piscataway, NJ); agarose; beads of polystyrene about 1 micron to about 5 millimeters in diameter available from Abbott Laboratories of North Chicago, IL; polyvinyl chloride, polystyrene, cross-linked polyacrylamide, nitrocellulose- or nylon-based webs such as sheets, strips or paddles; or tubes, plates or the wells of a microtiter plate such as those made from polystyrene or polyvinylchloride.

The NANBV structural protein, fusion protein, labeled specific binding agent or amplifying reagent of any diagnostic system described herein can be provided in solution, as a liquid dispersion or as a substantially dry power, e.g., in lyophilized form. Where the indicating means is an enzyme, the enzyme's substrate can also be provided in a separate package of a system. A solid support such as the before-described microtiter plate and one or more buffers can also be included as separately packaged elements in this diagnostic assay system.

The packages discussed herein in relation to diagnostic systems are those customarily utilized in

diagnostic systems. Such packages include glass and plastic (e.g., polyethylene, polypropylene and polycarbonate) bottles, vials, plastic and plastic-foil laminated envelopes and the like.

5 2. Diagnostic Methods

10 The present invention contemplates any diagnostic method that results in detecting anti-NANBV structural protein antibodies or NANBV structural antigens in a body fluid sample using a NANBV structural protein, fusion protein or anti-NANBV structural antigen antibody of this invention as an immunochemical reagent to form an immunoreaction product whose amount relates, either directly or indirectly, to the amount of material to be detected in the sample. Those skilled in the art will understand that there are numerous well known clinical diagnostic chemistry procedures in which an immunochemical reagent of this invention can be used to form an immunoreaction product whose amount relates to the amount of specific antibody or antigen present in a body sample.

20 Various heterogenous and homogenous protocols, either competitive or noncompetitive, can be employed in performing an assay method of this invention. Thus, while exemplary methods are described herein, the invention is not so limited.

25 To detect the presence of anti-NANBV structural protein antibodies in a patient, a bodily fluid sample such as blood, plasma, serum, urine or saliva from the patient is contacted by admixture under biological assay conditions with a NANBV structural protein, and preferably with a fusion protein of the present invention, to form an immunoreaction admixture. The admixture is then maintained for a period of time sufficient to allow the formation of a NANBV structural protein-antibody molecule immunoreaction product (immunocomplex). The presence, and preferably

the amount, of complex can then be detected as described herein. The presence of the complex is indicative of anti-NANBV antibodies in the sample.

5 In preferred embodiments the presence of the immunoreaction product formed between NANBV structural protein and a patient's antibodies is detected by using a specific binding reagent as discussed herein. For example, the immunoreaction product is first admixed with a labeled specific binding agent to form
10 a labeling admixture. A labeled specific binding agent comprises a specific binding agent and a label as described herein. The labeling admixture is then maintained under conditions compatible with specific binding and for a time period sufficient for any
15 immunoreaction product present to bind with the labeled specific binding agent and form a labeled product. The presence, and preferably amount, of labeled product formed is then detected to indicate the presence or amount of immunoreaction product.

20 In preferred embodiments the diagnostic methods of the present invention are practiced in a manner whereby the immunocomplex is formed and detected in a solid phase, as disclosed for the diagnostic systems herein.

25 Thus, in a preferred diagnostic method, the NANBV structural protein is affixed to a solid matrix to form the solid phase. It is further preferred that the specific binding agent is protein A, or an anti-human Ig, such as IgG or IgM, that can complex with
30 the anti-NANBV structural protein antibodies immunocomplexed in the solid phase with the NANBV structural protein. Most preferred is the use of labeled specific binding agents where the label is a radioactive isotope, an enzyme, biotin or a
35 fluorescence marker such as lanthanide as described

for the diagnostic systems, or detailed by references shown below.

In this solid phase embodiment, it is particularly preferred to use a recombinant protein that contains the antigen defined by the amino acid residue sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20, from residue 21 to residue 40, from residue 2 to residue 40, or from residue 1 to residue 74, as embodied in the fusion proteins as described in Example 7.

In another preferred diagnostic method, the NANBV structural protein of the invention is affixed to solid matrix as described above, and dilutions of the biological sample are subjected to the immunocomplexing step by contacting dilutions of sample with the solid surface and removing non-bound materials. Due to the multivalence of antibodies present in biological samples from infected individuals (bivalent for IgG, pentavalent for IgM) subsequent addition of labeled NANBV structural protein of the invention to this admixture will become attached to the solid phase by the sample antibody serving as bridge between the solid phase NANBV structural protein of the invention and the soluble, labeled NANBV structural protein. The presence of label in the solid phase indicates the presence and preferably the amount of specific antibody in the sample. One skilled in the art can determine a range of dilutions and determine therefrom a concentration of labeled antigen in the solid phase. The biological sample and the labeled NANBV structural protein of the invention can be admixed prior to, or simultaneously with contacting the biological sample with the solid phase allowing the trimolecular complex to form at the solid phase by utilizing the bridging property of bivalent or multivalent specific antibody. As a

particularly useful label, biotinylated NANBV structural protein of the invention can be the labeled antigen, allowing the subsequent detection by addition of an enzyme-streptavidin, or an enzyme-avidin
5 complex, followed by the appropriate substrate.

Enzymes such as horse-radish peroxidase, alkaline phosphatase, β -galactosidase or urease are frequently used and these, and other, along with several appropriate substrates are commercially available.

10 Preferred labels with a marker which allows direct detection of the formed complex include the use of a radioactive isotope, such as, eg., iodine, or a lanthanide chelate such as Europium.

In another embodiment designed to detect the
15 presence of a NANBV structural antigen in a body fluid sample from a patient, the sample (e.g. blood, plasma, serum, urine or saliva) is contacted by admixture under biological assay conditions with an anti-NANBV structural protein antibody of this invention, to form
20 an immunoreaction admixture. The admixture is then maintained for a period of time sufficient to allow the formation of a antigen-antibody immunoreaction product containing NANBV structural antigens complexed with an antibody of this invention. The presence and
25 preferably amount, of complex can then be determined, thereby indicating the presence of antigen in the body fluid sample.

In a preferred embodiment, the antibody is present in a solid phase. Still further preferred,
30 the amount of immunocomplex formed is measured by a competition immunoassay format where the antigen in a patient's body fluid sample competes with a labeled recombinant antigen of this invention for binding to the solid phase antibody. The method comprises
35 admixing a body fluid sample with (1) solid support having affixed thereto an antibody according to this

invention and (2) a labeled NANBV structural protein of this invention to form a competition immunoreaction admixture that has both a liquid phase and a solid phase. The admixture is then maintained for a time period sufficient to form a labeled NANBV structural protein-containing immunoreaction product in the solid phase. Thereafter, the amount of label present in the solid phase is determined, thereby indicating the amount of NANBV structural antigen in the body fluid sample.

Enzyme immunoassay techniques, whether direct or competition assays using homogenous or heterogenous assay formats, have been extensively described in the art. Exemplary techniques can be found in Maggio, Enzyme Immunoassay, CRC Press, Cleveland, OH (1981); and Tijssen, "Practice and Theory of Enzyme Immunoassays", Elsevier, Amsterdam (1988).

Biological assay conditions are those that maintain the biological activity of the NANBV structural protein and the anti-NANBV structural protein antibodies in the immunoreaction admixture. Those conditions include a temperature range of about 4C to about 45C, preferably about 37C, a pH value range of about 5 to about 9, preferably about 7, and an ionic strength varying from that of distilled water to that of about one molar sodium chloride, preferably about that of physiological saline. Methods for optimizing such conditions are well known in the art.

Also contemplated are immunological assays capable of detecting the presence of immunoreaction product formation without the use of a label. Such methods employ a "detection means", which means are themselves well-known in clinical diagnostic chemistry and constitute a part of this invention only insofar as they are utilized with otherwise novel polypeptides, methods and systems. Exemplary

detection means include methods known as biosensors and include biosensing methods based on detecting changes in the reflectivity of a surface (surface plasmon resonance), changes in the absorption of an evanescent wave by optical fibers or changes in the propagation of surface acoustical waves.

Another embodiment contemplates detection of the immunoreaction product employing time resolved fluorometry (TR-FIA), where the label used is able to produce a signal detectable by TR-FIA. Typical labels suitable for TR-FIA are metal-complexing agents such as a lanthanide chelate formed by a lanthanide and an aromatic beta-diketone, the lanthanide being bound to the antigen or antibody via an EDTA-analog so that a fluorescent lanthanide complex is formed.

The principle of time-resolved fluorescence is described by Soini et al, Clin. Chem., 25:353-361 (1979), and has been extensively applied to immunoassay. See for example, Halonen et al., Current Topics in Microbiology and Immunology, 104: 133-146 (1985); Suonpaa et al., Clinica Chimica Acta, 145:341-348 (1985); Lovgren et al., Talanta, 31:909-916 (1984); U.S. Patent Nos. 4,374,120 and 4,569,790; and published International Patent Application Nos. EPO 139 675 and W087/02708. A preferred lanthanide for use in TR-FIA is Europium.

Reagents and systems for practicing the TR-FIA technology are available through commercial suppliers (Pharmacia Diagnostics, Upsala, Sweden).

Particularly preferred are the solid phase immunoassays described herein in Example 7, performed as a typical "Western Blot".

The present diagnostic methods may be practiced in combination with other separate methods for detecting the appearance of anti-NANBV antibodies in species infected with NANBV. For example, a

composition of this invention may be used together with commercially available C-100-3 antigen (Ortho Diagnostics, Inc., Raritan, N.J.) in assays to determine the presence of either or both antibody species immunoreactive with the two antigens.

Examples

The following examples are given for illustrative purposes only and do not in any way limit the scope of the invention.

1. Production of Recombinant DNA Molecules

A. Isolation of NANBV Clones and Sequence Analysis

(1) Isolation of NANBV RNA and Preparation of cDNA

As a source for NANB virions, blood was collected from a chimpanzee infected with the Hutchinson (Hutch) strain exhibiting acute phase NANBH. Plasma was clarified by centrifugation and filtration. NANB virions were then isolated from the clarified plasma by immunoaffinity chromatography on a column of NANBV IgG (Hutch strain) coupled to protein G sepharose. NANBV RNA was eluted from the sepharose beads by soaking in guanidinium thiocyanate and the eluted RNA was then concentrated through a cesium chloride (CsCl) cushion. Sambrook et al., Molecular Cloning: A Laboratory Manual, Sambrook et al., eds. Second Edition, Cold Spring Harbor Laboratory Press, NY (1989).

The purified NANBV RNA was used as a template in a primer extension reaction admixture containing random and oligo dT primers, dNTP's, and reverse transcriptase to form first strand cDNAs. The resultant first strand cDNAs were used as templates for synthesis of second strand cDNAs in a reaction admixture containing DNA polymerase I and RNase H to

form double stranded (ds) cDNAs (Sambrook et al., supra). The synthesized ds cDNAs were amplified using an assymetric synthetic primer-adaptor system wherein sense and anti-sense primers were annealed to each other and ligated to the ends of the double stranded NANBV cDNAs with T4 ligase under blunt-end conditions to form cDNA-adaptor molecules. Polymerase chain reaction (PCR) amplification was performed by admixing the cDNA-adaptor molecules with the same positive sense adaptor primers, dNTP's and TAQ polymerase to prepare amplified NANBV cDNAs. The resultant amplified NANBV cDNA sequences were then used as templates for subsequent amplification in a PCR reaction with specific NANBV oligonucleotide primers.

(2) Synthesis of Oligonucleotides For Use in NANBV Cloning

Oligonucleotides were selected to correspond to the 5' sequence of Hepatitis C which putatively encodes the NANBV structural capsid and envelope proteins (HCJ1 sequence: Okamoto et al., Jap. J. Exp. Med., 60:167-177, 1990). The selected oligonucleotides were synthesized on a Pharmacia Gene Assembler according to the manufacturer's instruction, purified by polyacrylamide gel electrophoresis and have nucleotide base sequences as shown in Table 1.

TABLE 1

<u>Synthetic Oligonucleotides</u>		
Oligo-	Putative	
nucleotide	NANBV	Oligonucleotide
<u>Designation*</u>	<u>Region</u>	<u>Sequence</u>
690 (+)	Capsid 1-21	ATGAGCACGATTCCCAAACCT
693 (+)	Capsid 146-162	GAGGAAGACTTCCGAGC
694 (-)	Capsid 208-224	GTCCTGCCCTCGGGCCG
691 (-)	Capsid 340-360	ACCCAAATTGCGCGACCTACG
14 (+)	Envelope 356-374	TGGGTAAGGTCATCGATAC

15 (+) Envelope 361-377 AAGGTCATCGATACCCT
 18 (-) Envelope 512-529 AGATAGAGAAAGAGCAAC
 16 (-) Envelope 960-981 GGACCAGTTCATCATCATATAT
 17 (-) Envelope 957-976 CAGTTCATCATCATATCCCA

5

a The oligonucleotides are numerically defined and their polarity is indicated as (+) and (-) indicating the sequence corresponds to the sense and anti-sense coding strand, respectively. All sequences are listed in the 5' to 3' orientation.

10

(3) PCR Amplification of NANBV cDNA

PCR amplification was performed by admixing the primer-adapted amplified cDNA sequences prepared in Example 1A(1) with the synthetic oligonucleotides 690 and 694 as primer (primer pairs 690:694). The resulting PCR reaction admixture contained the primer-adapted amplified cDNA template, oligonucleotides 690 and 694, dNTP's, salts (KCl and MgCl₂) and TAQ polymerase. PCR amplification of the cDNA was conducted by maintaining the admixture at a 37 C annealing temperature for 30 cycles. Aliquots of samples from the first round of amplification were reamplified at a 55 C annealing temperature for 30 cycles under similar conditions.

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(4) Preparation of Vectors Containing PCR Amplified ds DNA

Aliquots from the second round of PCR amplification were subjected to electrophoresis on a 5% acrylamide gel. After separation of the PCR reaction products, the region of the gel containing DNA fragments corresponding to the expected 690:694 amplified product of approximately 224 bp was excised and purified following standard electroelution techniques (Sambrook et al., *supra*). The purified fragments were kinased and cloned into the pUC 18 plasmid cloning vector at the Sma I polylinker site to

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form a plasmid containing the DNA segment 690:694
operatively linked to pUC 18.

5 The resulting mixture containing pUC 18 and a DNA
segment corresponding to the 690:694 sequence region
was then transformed into the E. coli strain JM83.
Plasmids containing inserts were identified as lac-
(white) colonies on Xgal medium containing ampicillin.
pUC 18 plasmids which contained the 690:694 DNA
segment were identified by restriction enzyme analysis
10 and subsequent electrophoresis on agarose gels, and
were designated pUC 18 690:694 rDNA molecules.

(5) Sequencing of Hepatitis Clones
that Encode the Putative Capsid
Protein

15 Two independent colonies believed to
contain a pUC 18 vector having the NANBV Hutch strain
690:694 DNA segment (pUC 18 690:694) that codes for
the amino terminus of the putative capsid protein were
amplified and used to prepare plasmid DNA by CsCl
20 density gradient centrifugation by standard procedures
(Sambrook et al., supra). The plasmids were sequenced
using ³⁵S dideoxy procedures with pUC 18 specific
primers. The two plasmids were independently
sequenced on both DNA strands to assure the accuracy
25 of the sequence. The resulting sequence information
is presented as nucleotides 1-224 of SEQ. ID NO. 1.

Plasmid pUC 18 690:694 contains a NANBV DNA
segment that is 224 bp in length and when compared to
the HCJ1 prototype sequence reveals two nucleotide
30 substitutions and one amino acid residue difference in
the amino terminal region of the putative capsid
protein.

(6) Preparation of NANBV Clones from
the 5' End of the Genome

35 To obtain the sequence of the NANBV
Hutch genome encoding the remainder of the capsid

region (Okamoto et al., supra), the oligonucleotides 693 and 691 (described in Table 1) were used in PCR reactions. cDNA was prepared as described in Example 1A(1) to viral NANBV RNA from (Hutch) and used in PCR amplification as described in Example 1A(3) with the oligonucleotide pair 693:691. The resultant PCR amplified ds DNA was then cloned into pUC 18 cloning vectors and screened for inserts as described in Example 1A(4) to form pUC 18 693:691. Clones were then sequenced with pUC 18 specific primers as described in Example 1A(5).

Plasmid pUC 18 693:691 contains a NANBV DNA segment that is 157 bp in length and spans nucleotides 203-360 of SEQ.ID NO. 1. The clone is not complete to the 693 primer used for generating the fragment. The sequence of this fragment reveals three nucleotide differences when compared to the known sequence of HCJ1 and does not have any corresponding amino acid changes to the HCJ1 sequence.

To obtain the sequence of the NANBV Hutch genome encoding the putative envelope region (Okamoto et al., supra), the oligonucleotide primers 14 through 18 (described in Table 1) were used in various combinations with NANBV Hutch RNA samples. As a source of NANBV RNA, a liver biopsy specimen from a chimpanzee inoculated with the Hutch strain at 4 weeks post-inoculation and exhibiting acute infection was used. The biopsied sample was first frozen and then ground. The resultant powder was then subjected to treatment with guanidine isothiocyanate for the extraction of RNA. RNA was extracted from the guanidium treated liver samples with phenol in the presence of SDS at 65 C. The liver samples were extracted a second time, and subjected to extraction with chloroform. The extracted RNA was precipitated at -20 C with isopropanol and sodium acetate.

The purified liver-derived RNA was used as a template in primer extension reactions with the oligonucleotides 18 and 16 to generate NANBV specific-cDNAs. To prepare cDNA to the Hutch strain amino-terminal protein coding sequences, anti-sense oligonucleotides, 18 and 16, were annealed to liver-derived Hutch RNA in the presence of dNTPs and reverse transcriptase at 42 C to form primer extension products. The first round of PCR amplification of the two cDNAs was performed by admixing the primer extension reaction products with separate pairs of oligonucleotides 14:16 (16 primed cDNA) and 14:18 (18 primed cDNA) for 30 cycles at 55 C annealing temperature. The PCR reactions were performed on the above admixture as in 1A(3). Aliquots from the 14:16 and 14:18 amplifications were used as templates for the second round of amplification in which the oligonucleotide pairs 15:17 and 15:18, respectively, were used as primers.

PCR reaction products from each of the primer pair reactions were analyzed by electrophoresis on low melt agarose gels. Following separation, the regions of the gel containing DNA fragments corresponding to the expected 15:17 and 15:18 amplified products of approximately 617 bp and 168 bp, respectively, were excised and eluted from the gel slices at 65 C. The resultant eluted fragments were purified by phenol and chloroform extractions. To clone the 15:17 and 15:18 fragments, the purified fragments were separately treated with the Klenow fragment of DNA polymerase and kinase for subsequent subcloning into the Sma I site of the pBluescript plasmid vector (Stratagene Cloning Systems, La Jolla, CA). Transformed *E. coli* DH5 colonies were analyzed for plasmid insert by restriction enzyme analysis as described in Example 1A(4).

pBluescript plasmid containing 15:17 or 15:18 DNA segments were purified using large scale CsCl plasmid preparation protocols. The DNA segments present in the amplified and purified plasmids were each
5 sequenced as described in Example 1A(5).

The sequence of the 15:17 DNA segment is contained in SEQ. ID NO. 1 from nucleotide 361 to 978. The sequence of the 15:18 DNA segment is also presented in SEQ. ID NO. 1 from nucleotide 361 to 529.
10 These two clones overlap by 168 bp of the 15:18 DNA segment.

The sequence results indicate that the 15:17 DNA segment differs by 30 nucleotides when compared to the HcJ1 sequence (Okamoto et al., supra) and also differs
15 by ten amino acid residues. The 15:18 DNA segment differs by seven nucleotides and by three amino acid residues when compared to HcJ1. In the overlap region, the two DNA segments differ at two nucleotide bases, namely, bases 510 and 511, where DNA segment
20 15:18 contains a C in place of a T and an A in place of a G, respectively, which results in a change of a serine in place of a glycine amino acid residue, at residue 171 of SEQ. ID NO. 1. The reason for these differences is unknown and may be due to a PCR
25 artifact.

B. Production of Recombinant DNA (rDNA)
that Encodes a Fusion Protein

(1) Isolation of the 690:694
Fragment from the pUC 18 Clone and
30 Introduction of the Fragment into
the pGEX-3X Expression Vector

The pUC 18 vector containing the 690:694 DNA segment was subjected to restriction enzyme digestion with Eco RI and Bam HI to release the
35 DNA segment that includes a sequence contained in SEQ. ID NO. 1 from base 1 to base 224 from the pUC 18

vector. The released DNA segment was subjected to acrylamide electrophoresis and the DNA segment containing the 224 bp NANBV insert plus portions of the pUC 18 polylinker was then excised and eluted from the gel as described in Example 1A(4). The DNA segment was extracted with a mixture of phenol and chloroform, and precipitated.

The precipitated DNA segment was resuspended to a concentration of 25 ug/ml in water and treated with the Klenow fragment of DNA polymerase to fill in the staggered ends created by the restriction digestion. The resultant blunt-ended 690:694 segment was admixed with the bacterial expression vector, pGEX-3X, (available from Pharmacia Inc., Piscataway, NJ) which was linearized with the blunt end restriction enzyme Sma I. The admixed DNAs were then ligated by maintaining the admixture overnight at 16 C in the presence of ligase buffer and 5 units of T4 DNA ligase to form a plasmid of 690:694 DNA segment operatively linked to pGEX-3X.

(2) Selection and Verification of
Correct Orientation of Ligated
Insert

The ligation mixture containing the pGEX-3X vector and the 690:694 DNA segment was transformed into host E. coli strain W3110. Plasmids containing inserts were identified by selection of host bacteria containing vector in Luria broth (LB) media containing ampicillin. Bacterial cultures at stationary phase were subjected to alkaline lysis protocols to form a crude DNA preparation. The DNA was digested with the restriction enzyme Xho I. The single Xho I site, which cleaves within the 690:694 DNA segment between nucleotide position 173-178 of SEQ. ID NO. 1, but not within the pGEX-3X vector, was

used to screen for vector containing the 690:694 DNA segment.

Several 690:694 DNA segment-containing vectors were amplified and the resultant amplified vector DNA was purified by CsCl density gradient centrifugation. The DNA was sequenced across the inserted DNA segment ligation junctions by ³⁵S dideoxy methods with a primer which hybridized to the pGEX-3X sequence at nucleotide positions 614 to 633 contained in SEQ. ID NO. 2. Vectors containing 690:694 DNA segment having the correct coding sequence for in-frame translation of a NANBV structural protein were thus identified and selected to form pGEX-3X-690:694.

(3) Structure of the Fusion

Protein

The pGEX-3X vector is constructed to allow for inserts to be placed at the C terminus of Sj26, a 26-kDa glutathione S-transferase (GST; EC 2.5.1.18) encoded by the parasitic helminth Schistosoma japonicum. The insertion of the 690:694 NANBV fragment in-frame behind Sj26 allows for the synthesis of the Sj26-NANBV fusion polypeptide. The NANBV polypeptide can be cleaved from the GST carrier by digestion with the site-specific protease factor Xa (Smith et al., Gene, 67:31-40, 1988).

The nucleotide and predicted amino acid sequence of the pGEX-3X-690:694 fusion transcript from the GST sequence through the 690:694 insert is presented in SEQ. ID NO. 2. The resulting rDNA molecule, pGEX-3X-690:694, is predicted to encode a NANBV fusion protein having the amino acid residue sequence contained in SEQ. ID NO. 2 from amino acid residue 1 to residue 315. The resulting protein product generated from the expression of the plasmid is referred to as both the (GST:NANBV 690:694) fusion protein and the CAP-N fusion protein.

C. Production of Recombinant DNAs (rDNAs)
that Encode NANBV Capsid and Envelope
Fusion Proteins

pGEX-3X-693:691: Plasmid pGEX-3X-693:691
5 was formed by first subjecting the plasmid pUC 18
693:691 prepared in Example 1A(6) to restriction
enzyme digestion with Eco RI and Bam HI as performed
in Example 1B(1). The resultant released DNA segment
having a sequence contained in SEQ. ID NO. 1 from base
10 205 to base 360 was purified as performed in Example
1B(1). The purified DNA segment was admixed with and
ligated to the pGEX-3X vector which was linearized by
restriction enzyme digestion with Eco RI and Bam HI in
the presence of T₄ ligase at 16 C to form the plasmid
15 pGEX-3X-693:691.

A pGEX-3X plasmid containing a 693:691 DNA
segment was identified by selection Example 1B(2) with
the exception that crude DNA preparations were
digested with Eco RI and Bam HI to release the 693:691
20 insert. A pGEX-3X vector containing a 693:691 DNA
segment having the correct coding sequence for
in-frame translation of a NANBV structural protein was
identified by sequence analysis as performed in
Example 1B(2) and selected to form pGEX-3X-693:691.

25 The resulting vector encodes a fusion protein
(GST:NANBV 693:691) that is comprised of an
amino-terminal polypeptide portion corresponding to
residues 1-221 of GST as contained in SEQ. ID NO. 2,
an intermediate polypeptide portion corresponding to
30 residues 222-225 and defining a cleavage site for the
protease Factor Xa, a linker protein corresponding to
residues 226-230 consisting of the amino acid residue
sequence:

Gly Ile Pro Asn Ser
35 encoded by the nucleotide base sequence:
GGG ATC CCC AAT TCA, respectively;

a carboxy-terminal polypeptide portion corresponding to residues 231-282 defining a NANBV capsid antigen having the amino acid residue sequence 69-120 in SEQ. ID NO. 1, and a carboxy-terminal linker portion corresponding to residues 283-287 consisting of the amino acid residue sequence:

Asn Ser Ser END

encoded by the nucleotide base sequence:

AAT TCA TCG TGA, respectively.

10 pGEX-3X-15:18: Plasmid pGEX-3X-15:18 was formed by first subjecting the plasmid Bluescript 15:18 prepared in Example 1A(6) to restriction enzyme digestion with Eco RV and Bam HI and the Bam HI cohesive termini were filled in as performed in 15 Example 1B(1). The resultant released DNA segment having a sequence contained in SEQ. ID NO. 1 from base 361 to base 528 was purified as performed in Example 1B(1). The purified DNA segment was admixed with and 20 ligated to the pGEX-3X vector which was linearized by restriction enzyme digestion with Sma I as performed in 1B(1) to form the plasmid pGEX-3X-15:18.

25 A pGEX-3X plasmid containing a 15:18 DNA segment was identified by selection as performed in Example 1B(2) and crude DNA preparations were cut with Eco RI and Bam HI to release the 15:18 inserts. A pGEX-3X vector containing a 15:18 DNA segment having the correct coding sequence for in-frame translation of a NANBV structural protein was identified as performed in Example 1B(2) and selected to form pGEX-3X-15:18.

30 The resulting vector encodes a fusion protein (GST:NANBV 15:18) that is comprised of an amino-terminal polypeptide portion corresponding to residues 1-221 of GST, an intermediate polypeptide portion corresponding to residues 222-225 and defining 35 a cleavage site for the protease Factor Xa, a linker

protein corresponding to residues 226-234 consisting of the amino acid residue sequence:

Gly Ile Pro Ile Glu Phe Leu Gln Pro,
encoded by the nucleotide base sequence:

5 GGG ATC CCC ATC GAA TTC CTG CAG CCC,
respectively; a carboxy-terminal polypeptide portion
corresponding to residues 235-290 defining a NANBV
envelope antigen having the amino acid residue
sequence 121-176 in SEQ. ID NO. 1, and a
10 carboxy-terminal linker portion corresponding to
residues 291-298 consisting of a amino acid residue
sequence:

Trp Gly Ile Gly Asn Ser Ser END
encoded by the nucleotide base sequence:

15 TGG GGG ATC GGG AAT TCA TCG TGA, respectively.

pGEX-3X-15:17: Plasmid pGEX-3X-15:17 was
formed by first subjecting the plasmid Bluescript
15:17 prepared in Example 1A(6) to restriction enzyme
digestion with Eco RI and Bam HI and the cohesive
20 termini were filled in as performed in Example 1B(1).
The resultant released DNA segment having a sequence
contained in SEQ. ID NO. 1 from base 361 to base 978
was purified as performed in Example 1B(1). The
purified DNA segment was admixed with and ligated to
25 the pGEX-3X vector which was linearized by restriction
enzyme digestion with Sma I as performed in Example
1B(1) to form the plasmid pGEX-3X-15:17.

A pGEX-3X plasmid containing a 15:17 DNA segment
was identified by selection as performed in Example
30 1B(2) and DNA preparations were digested with Eco RI
and Bam HI as indicated above. pGEX-3X vector
containing a 15:17 DNA segment having the correct
coding sequence for in-frame translation of a NANBV
structural protein was identified as performed in
35 Example 1B(2) and selected to form pGEX-3X-15:17.

The resulting vector encodes a fusion protein (GST:NANBV 15:17) that is comprised of an amino-terminal polypeptide portion corresponding to residues 1-221 of GST, an intermediate polypeptide portion corresponding to residues 222-225 and defining a cleavage site for the protease Factor Xa, a linker protein corresponding to residues 226-233 consisting of the amino acid residue sequence:

Gly Ile Pro Asn Leu Arg Ser Pro

10 encoded by the nucleotide base sequence:

GGG ATC CCC AAT TCC TGC AGC CCT, respectively; a carboxy-terminal polypeptide portion corresponding to residues 234-439 defining a NANBV envelope antigen having the amino acid residue sequence 121-326 in SEQ.

15 ID NO. 1, and a carboxy-terminal linker portion corresponding to residues 440-446 consisting of the amino acid residue sequence:

Gly Ile Gly Asn Ser Ser END

encoded by the nucleotide base sequence:

20 GGG ATC GGG AAT TCA TCG TGA, respectively.

pGEX-2T-15:17: Plasmid pGEX-2T-15:17 was formed by first subjecting the plasmid Bluescript 15:17 prepared in Example 1A(6) to restriction enzyme digestion with Eco RV and Bam HI and the Bam HI cohesive termini were filled in as performed in Example 1B(1). The resultant released DNA segment having a sequence contained in SEQ. ID NO. 1 from base 361 to base 978 was purified as performed in Example 1B(1). The purified DNA segment was admixed with and 25 ligated to the pGEX-2T vector (Pharmacia, INC.) which was linearized by restriction enzyme digestion with Sma I as performed in Example 1B(1) to form the plasmid pGEX-2T-15:17.

30 A pGEX-2T plasmid containing a 15:17 DNA segment was identified by selection as performed in Example 1B(2) and by digestion of crude DNA preparations with

Eco RI and Bam HI. A pGEX-2T vector containing a 15:17 DNA segment having the correct coding sequence for in-frame translation of a NANBV structural protein was identified as performed in Example 1B(2) and selected to form pGEX-2T-15:17.

The resulting vector encodes a fusion protein (GST:NANBV 15:17) that is comprised of an amino-terminal polypeptide portion corresponding to residues 1-221 of GST, an intermediate polypeptide portion corresponding to residues 222-226 and defining a cleavage site for the protease Thrombin consisting of the amino acid residue sequence:

Val Pro Arg Gly Ser

encoded by the nucleotide base sequence:

GTT CCG CGT GGA TCC, respectively;

a linker protein corresponding to residues 227-233 consisting of an amino acid residue sequence:

Pro Ser Asn Leu Arg Ser Pro

encoded by a nucleotide base sequence:

CCA TCG AAT TCC TGC AGC CCT,

respectively; a carboxy-terminal polypeptide portion corresponding to residues 234-439 defining a NANBV envelope antigen, and a carboxy-terminal linker portion corresponding to residues 440-446 consisting of the amino acid residue sequence:

Gly Ile His Arg Asp END

encoded by the nucleotide base sequence

GGA ATT CAT CGT GAC TGA, respectively.

pGEX-3X-690:691: To obtain a DNA segment

corresponding to the NANBV Hutch sequence sequence shown from SEQ. ID NO. 1 from base 1 to base 360, the oligonucleotides 690:691 are used in PCR reactions as performed in Example 1A(6). The resultant PCR amplified ds DNA is then cloned into pUC 18 cloning vectors as described in Example 1A(4) to form pUC 18 690:691. Clones are then sequenced with pUC 18

primers as described in Example 1A(5) to identify a plasmid containing the complete sequence. The resulting identified plasmid is selected, is designated pUC 18 690:691, and contains a NANBV DNA segment that is 360 bp in length and spans nucleotides 1-360 of SEQ. ID NO. 1.

Plasmid pGEX-3X-690:691 is formed by first subjecting the plasmid pUC 18 690:691 to restriction enzyme digestion with Eco RI and Bam HI as performed in Example 1B(1). The resultant released DNA segment having a sequence contained in SEQ. ID NO. 1 from base 1 to base 360 with pUC 18 polylinker sequence is purified as performed in Example 1B(1). The purified DNA segment is admixed with and ligated to the pGEX-3X vector which is linearized by restriction enzyme digestion with Sma I as performed in Example 1B(1) to form the plasmid pGEX-3X-690:691.

A pGEX-3X plasmid containing a 690:691 DNA segment is identified by selection as performed in Example 1B(2). pGEX-3X vector containing a 690:691 DNA segment having the correct coding sequence for in-frame translation of a NANBV structural protein is identified as performed in Example 1B(2) and selected to form pGEX-3X-690:691.

The resulting vector encodes a fusion protein (GST:NANBV 690:691) that is comprised of an amino-terminal polypeptide portion corresponding to residues 1-221 of GST, an intermediate polypeptide portion corresponding to residues 222-225 and defining a cleavage site for the protease Factor Xa, a linker protein corresponding to residues 226-234 consisting of the amino acid residue sequence:

Gly Ile Pro Asn Ser Ser Ser Val Pro
 encoded by the nucleotide base sequence:
 GGG ATC CCC AAT TCG AGC TCG GTA CCC

respectively; a carboxy-terminal polypeptide portion corresponding to residues 235-355 defining a NANBV capsid antigen, and a carboxy-terminal linker portion corresponding to residues 356-363 consisting of the amino acid residue sequence:

Thr Gly Ile Gly Asn Ser Ser END

encoded by the nucleotide base sequence:

ACG GGG ATC GGG AAT TCA TCG TGA, respectively.

pGEX-2T-CAP-A: Oligonucleotides 1-20(+) and 1-20(-) for constructing the vector pGEX-2T-CAP-A for expressing the CAP-A fusion protein were prepared as described in Example 1A(2) having nucleotide base sequences corresponding to SEQ. ID NO. 7 and SEQ. ID NO. 8, respectively.

Oligonucleotides 1-20 (+) and 1-20 (-) were admixed in equal amounts with the expression vector pGEX-2T (Pharmacia) that had been predigested with Eco RI and Bam HI and maintained under annealing conditions to allow hybridization of the complementary oligonucleotides and to allow the cohesive termini of the resulting double-stranded (ds) oligonucleotide product to hybridize with pGEX-2T at the Eco RI and Bam HI cohesive termini. After ligation the resulting plasmid designated pGEX-2T-CAP-A contains a single copy of the ds oligonucleotide product and a structural gene coding for a fusion protein designated CAP-A having an amino acid residue sequence shown in SEQ. ID NO. 3 from residue 1 to residue 252.

The pGEX-2T vector is similar to the pGEX-3X vector described above, except that the resulting fusion protein is cleavable by digestion with the site specific protease thrombin.

pGEX-2T-CAP-B: Oligonucleotides 21-40(+) and 21-40(-) for constructing the vector pGEX-2T-CAP-B for expressing the CAP-B fusion protein were prepared as described in Example 1A(2) having nucleotide base

sequences corresponding to SEQ. ID NO. 9 and SEQ. ID NO. 10, respectively.

Oligonucleotides 21-40 (+) and 21-40 (-) were admixed in equal amounts with the pGEX-2T expression vector that had been predigested with Eco RI and Bam HI and maintained under annealing conditions to allow hybridization of the complementary oligonucleotides and to allow the cohesive termini of the resulting double-stranded oligonucleotide product to hybridize with pGEX-2T at the Eco RI and Bam HI cohesive termini. After ligation the resulting plasmid designated as pGEX-2T-CAP-B contains a single copy of the ds oligonucleotide product and contains a structural gene coding for a fusion protein designated CAP-B having an amino acid residue sequence shown in SEQ. ID NO. 4 from residue 1 to residue 252.

pGEX-2T-CAP C: Oligonucleotides 41-60(+) and 41-60(-) for constructing the vector pGEX-2T-CAP-C for expressing the CAP-C fusion protein were prepared as described in Example 1A(2) having nucleotide base sequences corresponding to SEQ. ID NO. 11 and SEQ. ID NO. 12, respectively.

Oligonucleotides 41-60 (+) and 41-60 (-) were admixed in equal amounts with the pGEX-2T expression vector that had been predigested with Eco RI and Bam HI and maintained under annealing conditions to allow hybridization of the complementary oligonucleotides and to allow the cohesive termini of the resulting double-stranded oligonucleotide product to hybridize with pGEX-2T at the Eco RI and Bam HI cohesive termini. After ligation the resulting plasmid designated as pGEX-2T-CAP-C contains a single copy of the double-stranded oligonucleotide product and contains a structural gene coding for a fusion protein designated CAP-C having an amino acid residue sequence shown in SEQ. ID NO. 5 from residue 1 to residue 252.

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new
↓
pGEX-2T-CAP-A-B: Oligonucleotides for
constructing the vector pGEX-2T-CAP-A-B for expressing
the CAP-A-B fusion protein were prepared as described
in Example 1A(2) having nucleotide base sequences
5 corresponding to SEQ. ID NO. 13 and SEQ. ID NO. 14,
respectively.

Oligonucleotides according to SEQ. ID NO. 13 and
SEQ. ID NO. 14 were admixed in equimolar amounts with
the plasmid pGEX-3X-690:694 described in Example
10 1B(2). The admixture was combined with the reagents
for a polymerase chain reaction (PCR) and the two
admixed oligonucleotides were used as primers on the
admixed pGEX-3X-690:694 as template in a PCR reaction
to form a PCR extension product consisting of a
15 double-stranded nucleic acid molecule that encodes the
amino acid residue sequence contained in SEQ. ID NO. 1
from residue 2 to 40 and also includes PCR-added
restriction sites for Bam HI at the 5' terminus and
Eco RI at the 3' terminus. The PCR extension product
20 was then cleaved with the restriction enzymes Bam HI
and Eco RI to produce cohesive termini on the PCR
extension product. The resulting product with
cohesive termini was admixed in equal amounts with the
pGEX-2T expression vector that had been predigested
25 with Eco RI and Bam HI and maintained under annealing
conditions to allow the cohesive termini of the
double-stranded PCR extension product to hybridize
with pGEX-2T at the Eco RI and Bam HI cohesive
termini. After ligation the resulting plasmid
30 designated pGEX-2T-CAP-A-B contains a single copy of
the double-stranded PCR extension product and contains
a structural gene coding for a fusion protein
designated CAP-A-B having an amino acid residue
sequence shown in SEQ. ID NO. 6 from residue 1 to
35 ↓ residue 271.

2. Expression of the NANBV 690:694 Fusion
Protein Using rDNA

The bacterial colonies which contain the pGEX-3X-690:694 plasmid in the correct orientation were selected to examine the properties of the fusion protein. Bacterial cultures of pGEX-3X-690:694 were grown to a stationary phase in the presence of ampicillin (50 ug/ml final concentration) at 37 C. This culture was inoculated at a 1:50 dilution into fresh LB medium at 37 C in the presence of ampicillin and maintained at 37 C. with agitation at 250 rpm until the bacteria reached an optical density of 0.5 when measured using a spectrometer with a 550 nm wavelength light source detector. Isopropylthio-beta-D-galactoside (IPTG) was then admixed to the bacterial culture at a final concentration of 1 mM to initiate (induce) the synthesis of the fusion protein under the control of the tac promoter in the pGEX-3X vector.

Beginning at zero time and at one hour intervals thereafter for three hours following admixture with IPTG (i.e., the induction phase), the bacterial culture was maintained as above to allow expression of recombinant protein. During this maintenance phase, the optical density of the bacterial culture was measured and 1 ml aliquots were removed for centrifugation. Each resultant cell pellet containing crude protein lysate was resuspended in Laemmli dye mix containing 1% beta-mercaptoethanol at a final volume of 50 microliters (ul) for each 0.5 OD 550 unit. Samples were boiled for 15 minutes and 10 ul of each sample was electrophoresed on a 10% SDS-PAGE Laemmli gel.

Other GST:NANBV fusion proteins were also expressed in bacteria by transformation with the

appropriate expression vector and induction as described above.

3. Detection of Expressed Fusion Proteins

To visualize the IPTG-induced fusion proteins, the Laemmli gels were stained with Coomassie Blue and destained in acetic acid and methanol. Induced proteins from separate clones were examined and compared on the basis of the increase of a protein band in the predicted size range from time zero to time three hours post-IPTG treatment. Expression of fusion protein was observed in clones that exhibited an increase from zero time in the intensity of a protein band corresponding to the fusion protein.

The GST:NANBV fusion proteins CAP-A, CAP-B, and CAP-C, when analyzed on a 12.5% PAGE Laemmli gel as described in Example 2, exhibited an apparent molecular weight of about 30,000 daltons.

4. Western Blot Analysis

Samples from IPTG inductions containing a GST:NANBV fusion protein of this invention were separated by gel electrophoresis and were transferred onto nitrocellulose for subsequent immunoblotting analysis. The nitrocellulose filter was admixed with antibody blocking buffer (20 mM sodium phosphate, pH 7.5, 0.5 M sodium chloride, 1% bovine serum albumin, and 0.05% Tween 40) for 3 to 12 hours at room temperature. Sera from humans or chimpanzees with NANB hepatitis believed to contain antibody immunoreactive with NANBV structural protein was diluted 1:500 in the antibody blocking buffer and admixed with the nitrocellulose and maintained for 12 hours at room temperature to allow the formation of an immunoreaction product on the solid phase. The nitrocellulose was then washed three times in excess volumes of antibody blocking buffer. The washes were followed by admixture of the nitrocellulose with 50 ul

of ^{125}I protein A (New England Nuclear, Boston, MA) at a 1:500 dilution in antibody blocking buffer for one hour at room temperature to allow the labeled protein A to bind to any immunoreaction product present in the solid phase on the nitrocellulose. The nitrocellulose was then washed as described herein, dried and exposed to X-ray film for one to three hours at -70°C in order to visualize the label and therefore any immunoreaction product on the nitrocellulose.

Results of the Western blot immunoassay are shown in Tables 2 through 7. Samples prepared using pGEX-3X vector that produces control GST were also prepared as above and tested using the Western blot procedure as a control. The expressed GST protein was not detectable as measured by immunoreactivity using the sera shown to immunoreact with a fusion protein of this invention (e.g., GST:NANBV 690:694 fusion protein).

5. Purification of Expressed GST:NANBV Fusion Proteins

Cultures of E. coli strain W3110 transformed with recombinant pGEX-3X-690:694 plasmids prepared in Example 2 were cultured for 3 hours following IPTG induction treatment. The cells were then centrifuged to form a bacterial cell pellet, the cells were resuspended in 1/200 culture volume in lysis buffer (MTPBS: 150 mM NaCl, 16 mM Na_2HPO_4 , 4 mM NaH_2PO_4 , pH 7.3), and the cell suspension was lysed with a French pressure cell. Triton X-100 was admixed to the cell lysate to produce a final concentration of 1%. The admixture was centrifuged at 50,000 X g for 30 minutes at 4°C . The resultant supernatant was collected and admixed with 2 ml of 50% (w/v) glutathione agarose beads (Sigma, St. Louis, MO) preswollen in MTPBS. After maintaining the admixture for 5 minutes at 25°C to allow specific affinity binding between GST and glutathione in the solid phase, the beads were

collected by centrifugation at 1000 X g and washed in MTPBS three times.

5 The GST:NANBV 690:694 fusion protein was eluted from the washed glutathione beads by admixture and incubation of the glutathione beads with 2 ml of 50 mM Tris HCl, pH 8.0, containing 5 mM reduced glutathione for 2 minutes at 25 degrees C to form purified GST:NANBV 690:694 fusion protein.

10 The above affinity purification procedure produced greater than 95% pure fusion protein as determined by SDS PAGE. That is, the purified protein was essentially free of procaryotic antigen and non-structural NANBV antigens as defined herein.

15 Alternatively, GST:NANBV 690:694 fusion protein was purified by anion exchange chromatography. Cultures were prepared as described above and cell pellets were resuspended in 8M guanidine and maintained overnight at 4 C to solubilize the fusion protein. The cell suspension was then applied to an S-300 sepharose chromatography column and peak
20 fractions containing the GST:NANBV 690:694 fusion protein were collected, pooled, dialyzed in 4 M urea and subjected to anion exchange chromatography to form purified fusion protein.

25 ↓ Other GST:NANBV fusion proteins described herein
new were also expressed in cultures of E.coli Strain W3110 as described above using the GST fusion protein vectors produced in Example 1 after their introduction by transformation into the E.coli host. After
30 induction and lysis of the cultures, the GST fusion proteins were purified as described above using glutathione agarose affinity chromatography to yield greater than 95% pure fusion protein as determined by SDS-PAGE. Thus, CAP-A, CAP-B and CAP-C fusion
35 proteins were all expressed and purified as above using the pGEX-2T-CAP-A vector, the pGEX-2T-CAP-B

vector, or the pGEX-2T-CAP-C vector, respectively, and CAP-A-B fusion protein is expressed and purified using the pGEX-2T-CAP-A-B vector.

6. Protease Cleavage of Purified GST:NANBV

690:694 Fusion Protein

Purified GST:NANBV 690:694 fusion protein prepared in Example 5 is subjected to treatment with activated Factor (Xa) (Sigma) to cleave the GST carrier from the NANBV 690:694 fusion protein (Smith et al., supra). Seven ug of Factor X are activated prior to admixture with purified fusion proteins by admixture and maintenance with 75 nanograms (ng) activation enzyme, 8 mM Tris HCl (pH 8.0), 70 mM NaCl and 8 mM CaCl₂ at 37 C for 5 minutes. Fifty ug of purified fusion protein are then admixed with 500 ng activated human factor Xa in the elution buffer described in Example 5 containing 50 mM Tris HCl, 5 mM reduced glutathione, 100 mM NaCl, and 1 mM CaCl₂, and maintained at 25 C for 30 minutes. The resulting cleavage reaction products are then absorbed on glutathione-agarose beads prepared in Example 5 to affinity bind and separate free GST from any cleaved NANBV structural antigen-containing protein. Thereafter the liquid phase is collected to form a solution containing purified NANBV structural protein having an amino acid residue sequence contained in SEQ. ID NO. 2 from residue 226 to residue 315.

7. Immunological Detection of Anti-NANBV

Structural Protein Antibodies

NANBV Hutch strain virus was injected in chimpanzees and blood samples were collected at various intervals to analyze the immunological response to NANBV by five different diagnostic assays. Chimpanzees were categorized as either being in the acute or chronic phase of infection. The assays utilized in the evaluation of the immune response

include: 1) alanine aminotransferase (ALT) enzyme detection (Alter et al., JAMA, 246:630-634, 1981; and Aach et al., N. Engl. J. Med., 304:989-994, 1981); 2) histological evaluation for NANBV virions by electron microscopy (EM); 3) detection of anti-HCV antibodies using the commercially available kit containing C-100-3 antigen (Ortho Diagnostics, Inc.); 4) detection of anti-CAP-N antibodies by immunoblot analysis as described in Example 4 (using the CAP-N fusion protein; and 5) Detection of virus by PCR amplification as described in Example 1.

In Table 2, results are presented from ALT, EM, anti-HCV, anti-CAP-N, and PCR assays on sera from a chimpanzee with acute NANB Hepatitis.

TABLE 2

CHIMP 59 - ACUTE NANB HEPATITIS

WEEK						PCR
	POST			ANTI	ANTI	
	<u>INNOC</u>	<u>ALT</u>	<u>EM</u>	<u>HCV</u>	<u>CAP-N</u> ¹	<u>690-691</u>
20	8	26	++	-	-	-
	10	26	+	-	+	-
	12	107	+	-	+	-
	14	115	+	+	+	-
25	16	26	+	+	+	+
	18	17	ND	+	+	(+)
	20	11	ND	+	+	-

¹ A plus (+) indicates immunoreaction was observed between admixed serum and the fusion protein, designated "CAP-N" because it corresponds to the amino terminal of the putative NANBV capsid protein, using the Western blot immunoassay described in Example 4.

The results in Table 2 show immunoreaction between fusion protein and anti-NANBV structural protein antibodies in the sera tested. Furthermore, seroconversion is detectable by the immunoassay using fusion protein containing capsid antigen at times earlier than when the same sera is assayed in the C-100-3-based immunoassay.

In Table 3, results are presented from ALT, anti-HCV and anti-CAP-N assays on sera collected from a human with definitive NANB Hepatitis.

TABLE 3

NYU - 169 - DEFINITIVE NANB HEPATITIS

Week	Post		Anti	Anti
	<u>Infect</u>	<u>ALT</u>	<u>HCV</u>	<u>CAP-N</u>
2		34	-	-
6		8	-	-
10		150	-	-
12		118	-	-
14		183	-	+
16		317	-	+
19		213	-	+
23		53	-	+

The results in Table 3 show that in the human series 169 seroconversion sera samples, the CAP-N antigen present in the fusion protein detects NANBV-specific antibodies as early as 14 weeks post inoculation, whereas the C-100-3-based immunoassay does not detect any anti-NANBV antibody at the times studied.

In Table 4, results are presented from ALT, EM, anti-HCV, and anti-CAP-N assays on sera from a chimpanzee with a self limited infection presented.

TABLE 4

CHIMP 213 - SELF LIMITED INFECTION

Week				
	Post	ALT	EM	Anti
	<u>Innoc</u>			<u>HCV</u>
5	4	24	+	-
	6	34	+	-
	8	38	+	-
10	13	28	ND	-
	16	25	ND	-
	18	23	ND	+
	20	25	-	+

15

The results in Table 4 show that the CAP-N antigen detects anti-NANBV antibodies earlier than the C-100-3 antigen when using sera sampled during the course of a self-limiting NANBV infection.

20

In Table 5, results are presented from ALT, anti-HCV and anti-CAP-N assays on sera from a chimpanzee that converted from an acute infection profile to a chronic one.

25

TABLE 5

CHIMP 10 - ACUTE/CHRONIC NANB HEPATITIS

Week				
	Post	Peak	Anti	Anti
	<u>Symptoms</u>	<u>Innoc</u>	<u>ALT</u>	<u>HCV</u>
30	acute	2	223	-
	chronic	40	223	+
	chronic	42	223	+
	chronic	44	223	+
	chronic	51	223	+

35

The results in Table 5 indicate that the CAP-N antigen preferentially detects anti-NANBV antibodies in acute stages of NANBV infection.

5 In Table 6, results are presented from ALT, EM, anti-HCV and anti-CAP-N assays on sera collected at various intervals from several chimpanzees with acute or chronic NANB Hepatitis.

TABLE 6

10 ADDITIONAL ACUTE SERA

	Week	Week	Peak	Anti	Anti
	Post	Post			
	Innoc	Alt Elev	ALT	HCV	CAP-N
	2	+1	73	-	+
15	14	+2	66	-	+
	6	+2	197	-	+
	11	+1	151	-	-
	8	+4	125	-	+
	15	+1	82	-	+
20	12	-4	73	ND	+

ADDITIONAL CHRONIC SERA

	156	+131	110	+	+
	156	-	89	+	+
25	160	-	89	+	+

30 The results in Table 6 indicate that the CAP-N antigen more often detected anti-NANBV antibodies in sera from acutely infected individuals than did the C 100-3 antigen.

35 The results of Tables 2-6 show that the NANBV structural protein of the invention, in the form of a fusion protein containing CAP-N antigen and produced by the vector pGEX-3X-690:694, detects antibodies in defined ^{serum} ~~sera~~ conversion series at times in an infected

patient or chimpanzee earlier than detectable by present state of the art methods using the C-100-3 antigen. In addition, the results show that CAP-N antigen is particularly useful to detect acute NANBV infection early in the infection.

Taken together, the results indicate that patients infected with NANBV contain circulating antibodies in their blood that are immunospecific for NANBV antigen designated herein as structural antigens, and particularly are shown to immunoreact with the putative capsid antigen defined by CAP-N. These antibodies are therefore referred to as anti-NANBV structural protein antibodies and are to be distinguished from the class of antibodies previously detected using the NANBV non-structural protein antigen C-100-3.

In Table 7, comparative results are presented from anti-HCV capsid fusion protein assays according to the basic immunoblot assay described in Example 4 using various chimp and human sera on the following HCV capsid fusion proteins: CAP-N, CAP-A, CAP-B and CAP-C.

TABLE 7

SERA	TYPE ^a	1-8.6				CAP-C ^e
		CAP-N ^b	CAP-A ^c	CAP-B ^d		
C18	Chimp 10 (A)	+++	+	+		-
C10	Chimp 194 (A)	+++	+++	+++		-
59-16	Chimp 59 (A)	+++	+	+++		ND
59-12	Chimp 59 (A)	ND ^f	++	+++		-
C9	Chimp 181 (A)	+++	-	+++		-
213-18	Chimp 213 (A)	ND	+	+		-
C2	Chimp 10 (C)	++	-	-		-
C1	Chimp 10 (C)	+++	-	-		-
C19	Chimp 10 (C)	+++	-	-		-
C4	Chimp 68 (C)	+++	+++	+++		ND

		N	I	D	C
169-16	Human	ND	+++	+++	-
169-23	Human	ND	+++	+++	-
191-1	Human	+	+	+	ND
191-2	Human	+	+	++	ND
191-3	Human	+	+	+	ND
216-1	Human	-	+/-	+/-	ND
216-2	Human	+	+	+	ND
216-3	Human	+	+	+	ND

- a The type of sera tested is indicated by the species (chimp or human), a chimp identification number if the sample is from a chimp, and a designation (in parenthesis) if the sera donor exhibits acute (A) or chronic (C) HCV infection at the time the sera was sampled.
- b CAP-N indicates the GST:NANBV 690:694 fusion protein produced in Example 5 that includes HCV capsid protein residues 1-74.
- c CAP-A indicates the GST:NANBV fusion protein produced in Example 5 that includes HCV capsid protein residues 1-20.
- d CAP-B indicates the GST:NANBV fusion protein produced in Example 5 that includes HCV capsid protein residues 21-40.
- e CAP-C indicates the GST:NANBV fusion protein produced in Example 5 that includes HCV capsid protein residues 41-60. *all neg.*
- f +, ++ and +++ indicate relative amounts of anti-HCV capsid antibody immunization product detected by the western blot assay, where + indicates a weak band after overnight exposure of the x-ray film, ++ indicates a strong band after overnight exposure of the x-ray film, +++ indicates a strong band after

1 to 2 hours exposure of the X-ray film, and
+/- or - indicates a faint or no band,
respectively, after overnight exposure of the
X-ray film

5 g "ND" indicates not tested.

The results shown in Table 7 indicate that fusion
proteins containing the CAP-A antigen or CAP-B antigen
are immunoreactive with antibodies present in sera from
10 HCV-infected humans or chimps. In addition, CAP-C
antigen does not significantly immunoreact with sera
from HCV infected humans or chimps.

The foregoing description and the examples are
intended as illustrative and are not to be taken as
15 limiting. Still other variations within the
spirit and scope of this invention are possible and
will readily present themselves to those skilled in the
art. Other embodiments are within the following
claims.

20

Description of The Sequence Listings

SEQ. ID NO. 1 contains the linear single-stranded
nucleotide base sequence of a preferred DNA segment of
the present invention that encodes portions of the
25 structural proteins of the Hutch strain of NANBV. The
base sequences are shown conventionally from left to
right and in the direction of 5' terminus to 3'
terminus using the single letter nucleotide base code
(A=adenine, T=thymine, C=cytosine and G=guanine) with
30 the position number of the first base residue in each
row indicated to the left of the row showing the
nucleotide base sequence.

The reading frame of the nucleotide sequence of
SEQ. ID NO. 1 is indicated by placement of the deduced
35 amino acid residue sequence of the protein for which it
codes below the nucleotide sequence such that the

triple letter code for each amino acid residue (Table of Correspondence) is located directly below the three bases (codon) coding for each residue. SEQ. ID NO. 1 also contains the linear amino acid residue sequence encoded by the nucleotide sequence of SEQ. ID NO. 1 and is shown conventionally from left to right and in the direction of amino terminus to carboxy terminus. The position number for the last amino acid residue in each row is indicated to the right of the row showing the amino acid residue sequence.

SEQ. ID NO. 2 contains the linear amino acid residue sequence of a preferred fusion protein designated CAP-N and is comprised of an amino-terminal polypeptide portion corresponding to residues 1-221 of glutathione-S-transferase, an intermediate polypeptide portion corresponding to residues 222-225 and defining a cleavage site for the protease Factor Xa, a linker portion corresponding to residues 226-234, a polypeptide portion corresponding to residues 235-308 defining a NANBV capsid antigen that has the amino acid residue sequence 1-74 in SEQ. ID NO. 1, and a carboxy-terminal linker portion corresponding to residues 309-315. SEQ. ID NO. 2 also contains the nucleotide base sequence of a linear single-stranded DNA segment that encodes the fusion protein described herein. The nomenclature and presentation of sequence information is as described for SEQ. ID NO. 1.

SEQ. ID NO. 3 contains the linear amino acid residue sequence of a preferred fusion protein designated CAP-A and comprised of an amino-terminal polypeptide portion corresponding to residues 1-220 of glutathione-S-transferase, an intermediate polypeptide portion corresponding to residues 221-226 and defining a cleavage site for the protease Thrombin, a polypeptide portion corresponding to residues 227-246 defining a portion of the NANBV capsid antigen that has

the amino acid residue sequence 1-20 in SEQ. ID NO. 1, and a carboxy-terminal linker portion corresponding to residues 247-252. SEQ. ID NO. 3 also contains the nucleotide base sequence of a linear single-stranded DNA segment that encodes the fusion protein described therein. The nomenclature and presentation of sequence information is as described for SEQ. ID NO. 1.

SEQ. ID NO. 4 contains the linear amino acid residue sequence of a preferred fusion protein designated CAP-B and comprised of an amino-terminal polypeptide portion corresponding to residues 1-220 of glutathione-S-transferase, an intermediate polypeptide portion corresponding to residues 221-226 and defining a cleavage site for the protease Thrombin, a polypeptide portion corresponding to residues 227-246 defining a portion of the NANBV capsid antigen that has the amino acid residue sequence 21-40 in SEQ. ID NO. 1, and a carboxy-terminal linker portion corresponding to residues 247-252. SEQ. ID NO. 4 also contains the nucleotide base sequence of a linear single-stranded DNA segment that encodes the fusion protein described therein. The nomenclature and presentation of sequence information is as described for SEQ. ID NO. 1.

SEQ. ID NO. 5 contains the linear amino acid residue sequence of a preferred fusion protein designated CAP-C and comprised of an amino-terminal polypeptide portion corresponding to residues 1-220 of glutathione-S-transferase, an intermediate polypeptide portion corresponding to residues 221-226 and defining a cleavage site for the protease Thrombin, a polypeptide portion corresponding to residues 227-246 defining a portion of the NANBV capsid antigen that has the amino acid residue sequence 41-60 in SEQ. ID NO. 1, and a carboxy-terminal linker portion corresponding to residues 247-252. SEQ. ID NO. 5 also contains the nucleotide base sequence of a linear single-stranded

DNA segment that encodes the fusion protein described therein. The nomenclature and presentation of sequence information is as described for SEQ. ID NO. 1.

SEQ. ID NO. 6 contains the linear amino acid residue sequence of a preferred fusion protein designated CAP-A-B and comprised of an amino-terminal polypeptide portion corresponding to residues 1-220 of glutathione-S-transferase, an intermediate polypeptide portion corresponding to residues 221-226 and defining a cleavage site for the protease Thrombin, a polypeptide portion corresponding to residues 227-265 defining a portion of the NANBV capsid antigen that has the amino acid residue sequence 2-40 in SEQ. ID NO. 1, and a carboxy-terminal linker portion corresponding to residues 266-271. SEQ. ID NO. 6 also contains the nucleotide base sequence of a linear single-stranded DNA segment that encodes the fusion protein described therein. The nomenclature and presentation of sequence information is as described for SEQ. ID NO. 1.

Sequence Listing

(1) Sequence Description: SEQ. ID NO. 1

1	ATGAGCACGATTCCCAAACCTCAAAGAAAAACCAAACGTAACACCAAC	
	MetSerThrIleProLysProGlnArgLysThrLysArgAsnThrAsn	16
49	CGTCGCCACAGGACGTCAAGTTCCCGGGTGGCGGTCAGATCGTTGGT	
	ArgArgProGlnAspValLysPheProGlyGlyGlyGlnIleValGly	32
97	GGAGTTTACTTGTTGCCGCGCAGGGGCCCTAGATTGGGTGTGCGCGCG	
	GlyValTyrLeuLeuProArgArgGlyProArgLeuGlyValArgAla	48
145	ACGAGGAAGACTTCGAGCGGTCGCAACCTCGAGGTAGACGTCAGCCT	
	ThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro	64
193	ATCCCCAAGGCACGTCGGCCCGAGGGCAGGACCTGGGCTCAGCCCGGG	
	IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGly	80

241 TACCCTTGGCCCCCTCTATGGCAATGAGGGTTGCGGGTGGGCGGGATGG 96
TyrProTrpProLeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrp

5 289 CTCCTGTCTCCCGTGGCTCTCGGCCTAGCTGGGGCCCCACAGACCCC 112
LeuLeuSerProArgGlySerArgProSerTrpGlyProThrAspPro

337 CGGCGTAGGTCGCGCAATTTGGGTAAGGTCATCGATACCCTTACGTGC 128
ArgArgArgSerArgAsnLeuGlyLysValIleAspThrLeuThrCys

10 385 GGCTTCGCCGACCTCATGGGGTACATACCGCTCGTCGGCGCCCCCTCTT 144
GlyPheAlaAspLeuMetGlyTyrIleProLeuValGlyAlaProLeu

433 GGAGGCGCTGCCAGGGCCCTGGCGCATGGCGTCCGGGTTCGGAAGAC 160
GlyGlyAlaAlaArgAlaLeuAlaHisGlyValArgValLeuGluAsp

15 481 GCGGTGAACTATGCAACAGGGAACCTTCCTGGTTGCTCTTTCTCTATC 176
GlyValAsnTyrAlaThrGlyAsnLeuProGlyCysSerPheSerIle

20 529 TTCCTTCTGGCCCTGCTCTCTTGCCCTGACTGTGCCCGCTTCAGCCTAC 192
PheLeuLeuAlaLeuLeuSerCysLeuThrValProAlaSerAlaTyr

577 CAAGTGC GCAATTCCTCGGGGCTTTACCATGTCACCAATGATTGCCCT 208
GlnValArgAsnSerSerGlyLeuTyrHisValThrAsnAspCysPro

25 625 AACTCGAGTGTGTGTACGAGGCGGCCGATGCCATCCTGCACACTCCG 224
AsnSerSerValValTyrGluAlaAlaAspAlaIleLeuHisThrPro

673 GGGTGTGTCCCTTGCCTTCGCGAGGGTAACGCCTCGAGGTGTTGGGTG 240
GlyCysValProCysValArgGluGlyAsnAlaSerArgCysTrpVal

30 721 GCGGTGACCCCCACGGTGGCCACCAGGGACGGCAAAC TCCCCACAACG 256
AlaValThrProThrValAlaThrArgAspGlyLysLeuProThrThr

35 769 CAGCTTCGACGTCATATCGATCTGCTTGTCGGGAGCGCCACCCTCTGC 272
GlnLeuArgArgHisIleAspLeuLeuValGlySerAlaThrLeuCys

817 TCGGCCCTCTACGTGGGGGACCTGTGCGGGTCTGTCTTTCTTGTGGT
 SerAlaLeuTyrValGlyAspLeuCysGlySerValPheLeuValGly 288

 5 865 CAACTGTTTACCTTCTCTCCAGGCGCCACTGGACGACGCAAGACTGC
 GlnLeuPheThrPheSerProArgArgHisTrpThrThrGlnAspCys 304

 913 AATTGTTCTATCTATCCCGGCCATATAACGGGTCATCGCATGGCATGG
 AsnCysSerIleTyrProGlyHisIleThrGlyHisArgMetAlaTrp 320

 10 961 GATATGATGATGAACTGG
 AspMetMetMetAsnTrp 326

 (2) Sequence Description: SEQ ID NO. 2
 15 1 ATGTCCCCTATACTAGGTTATTGGAAAATTAAGGGCCTTGTGCAACCC
 MetSerProIleLeuGlyTyrTrpLysIleLysGlyLeuValGlnPro 16

 49 ACTCGACTTCTTTTGAATATCTTGAAGAAAAATATGAAGAGCATTG
 ThrArgLeuLeuLeuGluTyrLeuGluGluLysTyrGluGluHisLeu 32

 20 97 TATGAGCGCGATGAAGGTGATAAATGGCGAAACAAAAGTTTGAATTG
 TyrGluArgAspGluGlyAspLysTrpArgAsnLysLysPheGluLeu 48

 145 GGT TTGGAGTTTCCCAATCTTCCTTATTATATTGATGGTGATGT TAAA
 25 GlyLeuGluPheProAsnLeuProTyrTyrIleAspGlyAspValLys 64

 193 TTAACACAGTCTATGGCCATCATACGTTATATAGCTGACAAGCACAAAC
 LeuThrGlnSerMetAlaIleIleArgTyrIleAlaAspLysHisAsn 80

 30 241 ATGTTGGGTGGTTGTCCAAAAGAGCGTGCAGAGATTTCAATGCTTGAA
 MetLeuGlyGlyCysProLysGluArgAlaGluIleSerMetLeuGlu 96

 289 GGAGCGGTTTTGGATATTAGATACGGTGTTCGAGAATTGCATATAGT
 GlyAlaValLeuAspIleArgTyrGlyValSerArgIleAlaTyrSer 112

 35 337 AAAGACTTTGAAACTCTCAAAGTTGATTTTCTTAGCAAGCTACCTGAA

LysAspPheGluThrLeuLysValAspPheLeuSerLysLeuProGlu 128
 385 ATGCTGAAAATGTTCTGAAGATCGTTTATGTCATAAAACATATTTAAAT
 MetLeuLysMetPheGluAspArgLeuCysHisLysThrTyrLeuAsn 144
 5 433 GGTGATCATGTAACCCATCCTGACTTCATGTTGTATGACGCTCTTGAT
 GlyAspHisValThrHisProAspPheMetLeuTyrAspAlaLeuAsp 160
 481 GTTGTTTTTATACATGGACCCAATGTGCCTGGATGCGTTCCCAAAATTA
 10 ValValLeuTyrMetAspProMetCysLeuAspAlaPheProLysLeu 176
 529 GTTTGTTTTAAAAAACGTATTGAAGCTATCCCACAAATTGATAAGTAC
 ValCysPheLysLysArgIleGluAlaIleProGlnIleAspLysTyr 192
 15 577 TTGAAATCCAGCAAGTATATAGCATGGCCTTTGCAGGGCTGGCAAGCC
 LeuLysSerSerLysTyrIleAlaTrpProLeuGlnGlyTrpGlnAla 208
 625 ACGTTTGGTGGTGGCGACCATCCTCCAAAATCGGATCTGATCGAAGGT
 ThrPheGlyGlyGlyAspHisProProLysSerAspLeuIleGluGly 224
 20 673 CGTGGGATCCCCAATTCGAGCTCGGTACCCATGAGCACGATTCCCAAA
 ArgGlyIleProAsnSerSerSerValProMetSerThrIleProLys 240
 721 CCTCAAAGAAAAACCAAACGTAACACCAACCGTCGCCCACAGGACGTC
 25 ProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspVal 256
 769 AAGTTCCCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTTGCCG
 LysPheProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuPro 272
 30 817 CGCAGGGGCCCTAGATTGGGTGTGCGCGACGAGGAAGACTTCCGAG
 ArgArgGlyProArgLeuGlyValArgAlaThrArgLysThrSerGlu 288
 865 CGGTCGCAACCTCGAGGTAGACGTCAGCCTATCCCCAAGGCACGTCGG
 ArgSerGlnProArgGlyArgArgGlnProIleProLysAlaArgArg 304
 35 913 CCCGAGGGCAGGACGGGGATCGGGAATTCATCGTGA

ProGluGlyArgThrGlyIleGlyAsnSerSerEnd 315

(3) Sequence Description: SEQ ID NO. 3

5	1	ATGTCCCCTATACTAGGTTATTGGAAAATTAAGGGCCTTGTGCAACCC	
		MetSerProIleLeuGlyTyrTrpLysIleLysGlyLeuValGlnPro	16
	49	ACTCGACTTCTTTTGGAAATATCTTGAAGAAAAATATGAAGAGCATTG	
		ThrArgLeuLeuLeuGluTyrLeuGluGluLysTyrGluGluHisLeu	32
10	97	TATGAGCGCGATGAAGGTGATAAATGGCGAAACAAAAAGTTTGAATTG	
		TyrGluArgAspGluGlyAspLysTrpArgAsnLysLysPheGluLeu	48
	145	GGTTTGGAGTTTCCCAATCTTCCTTATTATATTGATGGTGATGTTAAA	
		GlyLeuGluPheProAsnLeuProTyrTyrIleAspGlyAspValLys	64
15			
	193	TTAACACAGTCTATGGCCATCATACGTTATATAGCTGACAAGCACAAC	
		LeuThrGlnSerMetAlaIleIleArgTyrIleAlaAspLysHisAsn	80
	241	ATGTTGGGTGGTTGTCCAAAAGAGCGTGCAGAGATTTCATGCTTGAA	
20		MetLeuGlyGlyCysProLysGluArgAlaGluIleSerMetLeuGlu	96
	289	GGAGCGGTTTTGGATATTAGATACGGTGTTCGAGAATTGCATATAGT	
		GlyAlaValLeuAspIleArgTyrGlyValSerArgIleAlaTyrSer	112
25	337	AAAGACTTTGAACTCTCAAAGTTGATTTTCTTAGCAAGCTACCTGAA	
		LysAspPheGluThrLeuLysValAspPheLeuSerLysLeuProGlu	128
	385	ATGCTGAAAATGTTTGAAGATCGTTTATGTCATAAACATATTTAAAT	
30		MetLeuLysMetPheGluAspArgLeuCysHisLysThrTyrLeuAsn	144
	433	GGTGATCATGTAACCCATCCTGACTTCATGTTGTATGACGCTCTTGAT	
		GlyAspHisValThrHisProAspPheMetLeuTyrAspAlaLeuAsp	160
	481	GTTGTTTTATACATGGACCCAATGTGCCTGGATGCGTTCCCAAATTA	
35		ValValLeuTyrMetAspProMetCysLeuAspAlaPheProLysLeu	176

529 GTTGTGTTTTAAAAACGTATTGAAGCTATCCACAAATTGATAAGTAC
ValCysPheLysLysArgIleGluAlaIleProGlnIleAspLysTyr 192

577 TTGAAATCCAGCAAGTATATAGCATGGCCTTTGCAGGGCTGGCAAGCC
5 LeuLysSerSerLysTyrIleAlaTrpProLeuGlnGlyTrpGlnAla 208

625 ACGTTTGGTGGTGGCGACCATCCTCCAAAATCGGATCTGGTTCCGCGT
ThrPheGlyGlyGlyAspHisProProLysSerAspLeuValProArg 224

10 673 GGATCCATGAGCACGATTCCCAAACCTCAAAGAAAAACCAAACGTAAC
GlySerMetSerThrIleProLysProGlnArgLysThrLysArgAsn 240

721 ACCAACCGTCGCCCACAGGAATTCATCGTGA CTGACTGA
ThrAsnArgArgProGlnGluPheIleValThrAspEnd 252

15 (4) Sequence Description: SEQ. ID NO. 4

1 ATGTCCCCTATACTAGGTTATTGGAAAATTAAGGGCCTTGTGCAACCC
MetSerProIleLeuGlyTyrTrpLysIleLysGlyLeuValGlnPro 16

20 49 ACTCGACTTCTTTTGAATATCTTGAAGAAAAATATGAAGAGCATTTG
ThrArgLeuLeuLeuGluTyrLeuGluGluLysTyrGluGluHisLeu 32

97 TATGAGCGCGATGAAGGTGATAAATGGCGAAACAAAAAGTTTGAATTG
TyrGluArgAspGluGlyAspLysTrpArgAsnLysLysPheGluLeu 48

25 145 GGTTTGGAGTTTCCCAATCTTCCTTATTATATTGATGGTGATGTTAAA
GlyLeuGluPheProAsnLeuProTyrTyrIleAspGlyAspValLys 64

193 TTAACACAGTCTATGGCCATCATACGTTATATAGCTGACAAGCACAAC
30 LeuThrGlnSerMetAlaIleIleArgTyrIleAlaAspLysHisAsn 80

241 ATGTTGGGTGGTTGTCCAAAAGAGCGTGCAGAGATTTC AATGCTTGAA
MetLeuGlyGlyCysProLysGluArgAlaGluIleSerMetLeuGlu 96

35 289 GGAGCGGTTTTGGATATTAGATACGGTGTTCGAGAATTGCATATAGT
GlyAlaValLeuAspIleArgTyrGlyValSerArgIleAlaTyrSer 112

337 AAAGACTTTGAAACTCTCAAAGTTGATTTTCTTAGCAAGCTACCTGAA
 LysAspPheGluThrLeuLysValAspPheLeuSerLysLeuProGlu 128

 5 385 ATGCTGAAAATGTTCTGAAGATCGTTTATGTCATAAAACATATTTAAAT
 MetLeuLysMetPheGluAspArgLeuCysHisLysThrTyrLeuAsn 144

 433 GGTGATCATGTAACCCATCCTGACTTCATGTTGTATGACGCTCTTGAT
 GlyAspHisValThrHisProAspPheMetLeuTyrAspAlaLeuAsp 160
 10
 481 GTTGTTTTATACATGGACCCAATGTGCCTGGATGCGTTCCCAAATTA
 ValValLeuTyrMetAspProMetCysLeuAspAlaPheProLysLeu 176

 529 GTTTGTTTTAAAAACGTATTGAAGCTATCCCACAAATTGATAAGTAC
 15 ValCysPheLysLysArgIleGluAlaIleProGlnIleAspLysTyr 192

 577 TTGAAATCCAGCAAGTATATAGCATGGCCTTTGCAGGGCTGGCAAGCC
 LeuLysSerSerLysTyrIleAlaTrpProLeuGlnGlyTrpGlnAla 208

 20 625 ACGTTTGGTGGTGGCGACCATCCTCCAAAATCGGATCTGGTTCCGCGT
 ThrPheGlyGlyGlyAspHisProProLysSerAspLeuValProArg 224

 673 GGATCCGACGTCAAGTTCCCGGGTGGCGGTCAGATCGTTGGTGGAGTT
 GlySerAspValLysPheProGlyGlyGlyGlnIleValGlyGlyVal 240
 25
 721 TACTTGTTGCCGCGCAGGGAATTCATCGTGA CTGACTGA
 TyrLeuLeuProArgArgGluPheIleValThrAspEnd 252

 (5) Sequence Description: SEQ. ID NO. 5
 30 1 ATGTCCCCTATACTAGGTTATTGGAAAATTAAGGGCCTTG TGCAACCC
 MetSerProIleLeuGlyTyrTrpLysIleLysGlyLeuValGlnPro 16

 49 ACTCGACTTCTTTTGAATATCTTGAAGAAAAATATGAAGAGCATTTG
 ThrArgLeuLeuLeuGluTyrLeuGluGluLysTyrGluGluHisLeu 32
 35
 97 TATGAGCGCGATGAAGGTGATAAATGGCGAAACAAAAAGTTTGAATTG

TyrGluArgAspGluGlyAspLysTrpArgAsnLysLysPheGluLeu 48
 145 GGTTCGGAGTTTCCCAATCTTCCTTATTATATTGATGGTGATGTTAAA
 GlyLeuGluPheProAsnLeuProTyrTyrIleAspGlyAspValLys 64
 5 193 TTAACACAGTCTATGGCCATCATACGTTATATAGCTGACAAGCACAAC
 LeuThrGlnSerMetAlaIleIleArgTyrIleAlaAspLysHisAsn 80
 241 ATGTTGGGTGGTTGTCCAAAAGAGCGTGCAGAGATTCAATGCTTGAA
 10 MetLeuGlyGlyCysProLysGluArgAlaGluIleSerMetLeuGlu 96
 289 GGAGCGGTTTTGGATATTAGATACGGTGTTCGAGAATTGCATATAGT
 GlyAlaValLeuAspIleArgTyrGlyValSerArgIleAlaTyrSer 112
 15 337 AAAGACTTTGAACTCTCAAAGTTGATTTTCTTAGCAAGCTACCTGAA
 LysAspPheGluThrLeuLysValAspPheLeuSerLysLeuProGlu 128
 385 ATGCTGAAAATGTTCTGAAGATCGTTTATGTCATAAAACATATTTAAAT
 MetLeuLysMetPheGluAspArgLeuCysHisLysThrTyrLeuAsn 144
 20 433 GGTGATCATGTAACCCATCCTGACTTCATGTTGTATGACGCTCTTGAT
 GlyAspHisValThrHisProAspPheMetLeuTyrAspAlaLeuAsp 160
 481 GTTGTTTTTATACATGGACCCAATGTGCCTGGATGCGTTCCCAAATTA
 25 ValValLeuTyrMetAspProMetCysLeuAspAlaPheProLysLeu 176
 529 GTTTGTTTTTAAAAACGTATTGAAGCTATCCACAAATTGATAAGTAC
 ValCysPheLysLysArgIleGluAlaIleProGlnIleAspLysTyr 192
 30 577 TTGAAATCCAGCAAGTATATAGCATGGCCTTTGCAGGGCTGGCAAGCC
 LeuLysSerSerLysTyrIleAlaTrpProLeuGlnGlyTrpGlnAla 208
 625 ACGTTTGGTGGTGGCGACCATCCTCCAAAATCGGATCTGGTTCCGCGT
 ThrPheGlyGlyGlyAspHisProProLysSerAspLeuValProArg 224
 35 673 GGATCCGGCCCTAGATTGGGTGTGCGCGACGAGGAAGACTTCCGAG

GlySerGlyProArgLeuGlyValArgAlaThrArgLysThrSerGlu 240

721 CGGTCGCAACCTCGAGGTGAATTCATCGTGACTGACTGA
ArgSerGlnProArgGlyGluPheIleValThrAspEnd 252

5

(6) Sequence Description: SEQ. ID NO. 6

1 ATGTCCCTATACTAGGTTATTGGAAAATTAAGGGCCTTGTGCAACCC
MetSerProIleLeuGlyTyrTrpLysIleLysGlyLeuValGlnPro 16

10 49 ACTCGACTTCTTTTGGAAATATCTTGAAGAAAAATATGAAGAGCATTG
ThrArgLeuLeuLeuGluTyrLeuGluGluLysTyrGluGluHisLeu 32

97 TATGAGCGCGATGAAGGTGATAAATGGCGAAACAAAAAGTTTGAATTG
TyrGluArgAspGluGlyAspLysTrpArgAsnLysLysPheGluLeu 48

15 145 GGTTTGGAGTTTCCCAATCTTCCTTATTATATTGATGGTGATGTTAAA
GlyLeuGluPheProAsnLeuProTyrTyrIleAspGlyAspValLys 64

193 TTAACACAGTCTATGGCCATCATACGTTATATAGCTGACAAGCACAAC
LeuThrGlnSerMetAlaIleIleArgTyrIleAlaAspLysHisAsn 80

20 241 ATGTTGGGTGGTTGTCCAAAAGAGCGTGCAGAGATTTCATGCTTGAA
MetLeuGlyGlyCysProLysGluArgAlaGluIleSerMetLeuGlu 96

25 289 GGAGCGGTTTTGGATATTAGATACGGTGTTCGAGAATTGCATATAGT
GlyAlaValLeuAspIleArgTyrGlyValSerArgIleAlaTyrSer 112

337 AAAGACTTTGAACTCTCAAAGTTGATTTTCTTAGCAAGCTACCTGAA
LysAspPheGluThrLeuLysValAspPheLeuSerLysLeuProGlu 128

30 385 ATGCTGAAAATGTTCTGAAGATCGTTTATGTCATAAACATATTTAAAT
MetLeuLysMetPheGluAspArgLeuCysHisLysThrTyrLeuAsn 144

433 GGTGATCATGTAACCCATCCTGACTTCATGTTGTATGACGCTCTTGAT
GlyAspHisValThrHisProAspPheMetLeuTyrAspAlaLeuAsp 160

35

481 GTTGT TTTATACATGGACCCAATGTGCCTGGATGCGTTCCCAAATTA
ValValLeuTyrMetAspProMetCysLeuAspAlaPheProLysLeu 176

529 GTTGT TTTTAAAAACGTATTGAAGCTATCCACAAATTGATAAGTAC
5 ValCysPheLysLysArgIleGluAlaIleProGlnIleAspLysTyr 192

577 TTGAAATCCAGCAAGTATATAGCATGGCCTTTGCAGGGCTGGCAAGCC
LeuLysSerSerLysTyrIleAlaTrpProLeuGlnGlyTrpGlnAla 208

10 625 ACGTTTGGTGGTGGCGACCATCCTCCAAAATCGGATCTGGTTCCGCGT
ThrPheGlyGlyGlyAspHisProProLysSerAspLeuValProArg 224

673 GGATCCAGCACGATTCCCAAACCTCAAAGAAAAACCAAACGTAACACC
GlySerSerThrIleProLysProGlnArgLysThrLysArgAsnThr 240
15

721 AACCGTCGCCACAGGACGTCAAGTTCCCGGGTGGCGGTGAGATCGTT
AsnArgArgProGlnAspValLysPheProGlyGlyGlyGlnIleVal 256

769 GGTGGAGTTTACTTGTGTCGCGCAGGGAATTCATCGTGAAGTGA
20 GlyGlyValTyrLeuLeuProArgArgGluPheIleValThrAspEnd 271

(7) Sequence Description: SEQ. ID NO. 7
5'-GATCCATGAGCACGATTCCCAAACCTCAAAGAAAAACCAAACGTAACACCAACCGTCGC
CCACAGG-3'

25 (8) Sequence Description: SEQ. ID NO. 8
5'-AATTCCTGTGGGCGACGGTTGGTGTACGTTTGGTTTTCTTTGAGGTTTGGGAATCGT
GCTCATG-3'

(9) Sequence Description: SEQ. ID NO. 9
5'-GATCCGACGTCAAGTTCCCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTGCGG
30 CGCAGGG-3'

(10) Sequence Description: SEQ. ID NO. 10
5'-AATTCCTGCGCGGCAACAAGTAACTCCACCAACGATCTGACCGCCACCGGGAACTT
GACGTG-3'

(11) Sequence Description: SEQ. ID NO. 11
35 5'-GATCCGGCCCTAGATTGGGTGTGCGCGGACGAGGAAGACTTCCGAGCGGTGCGAACCT
CGAGGTG-3'

(12) Sequence Description: SEQ. ID NO. 12

5'-AATTCACCTCGAGGTTGCGACCGCTCGGAAGTCTTCCTCGTCGCGCGCACACCCAATCT
AGGGCCG-3'

(13) Sequence Description: SEQ. ID NO. 13

5 5'-GAATTCTTACCTGCGCGGCAACAAGTAAACTC-3'

(14) Sequence Description: SEQ. ID NO. 14

5'-GCTGGATCCAGCACGATTCCCAAACCTCAAAG-3'

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What Is Claimed Is:

1. A purified DNA segment comprising a nucleotide base sequence that encodes a NANBV structural protein having an amino acid residue sequence that includes an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20.
2. A purified DNA segment comprising a nucleotide base sequence that encodes a NANBV structural protein having an amino acid residue sequence that includes an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 21 to residue 40.
3. A purified DNA segment comprising a nucleotide base sequence that encodes a NANBV structural protein having an amino acid residue sequence that includes an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 2 to residue 40.
4. A recombinant DNA molecule comprising a vector operatively linked to a DNA segment according to claim 1.
5. The recombinant DNA molecule of claim 4 wherein said vector is an expression vector and said molecule is capable of expressing said protein in a compatible host.
6. The recombinant DNA molecule of claim 5 wherein said molecule encodes a NANBV structural protein having an amino acid residue sequence contained in SEQ. ID NO. 3 from residue 1 to residue 252.
7. A recombinant DNA molecule comprising a vector operatively linked to a DNA segment according to claim 2.
8. The recombinant DNA molecule of claim 7 wherein said vector is an expression vector and said molecule is capable of expressing said protein in a compatible host.
9. The recombinant DNA molecule of claim 8 wherein said molecule encodes a NANBV structural protein having an amino acid residue sequence contained in SEQ. ID NO. 4 from residue 1 to residue 252.
10. A recombinant DNA molecule comprising a vector operatively linked to a DNA segment according to claim 3.

11. The recombinant DNA molecule of claim 10 wherein said vector is an expression vector and said molecule is capable of expressing said protein in a compatible host.

12. The recombinant DNA molecule of claim 11 wherein said molecule encodes a NANBV structural protein having an amino acid residue sequence contained in SEQ. ID NO. 6 from residue 1 to residue 271.

13. A transformed cell culture comprising a nutrient medium containing a procaryotic host cell transformed with a recombinant DNA molecule according to claim 5, 8, or 11.

14. A method of producing a NANBV structural protein comprising:

a) initiating a culture comprising a nutrient medium containing host cells transformed with a recombinant DNA molecule according to claim 5, 8, or 11;

b) maintaining the culture for a time period sufficient for the host cell to express NANBV structural protein; and

c) recovering the NANBV structural protein from the culture.

15. An isolated NANBV structural protein comprising an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20.

16. The NANBV structural protein of claim 15 wherein said protein includes an amino acid residue sequence contained in SEQ. ID NO. 3 from residue 1 to residue 252.

17. An isolated NANBV structural protein comprising an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 21 to residue 40.

18. The NANBV structural protein of claim 17 wherein said protein includes an amino acid residue sequence contained in SEQ. ID NO. 4 from residue 1 to residue 252.

19. An isolated NANBV structural protein comprising an amino acid residue sequence contained in SEQ. ID NO. 1 from residue 2 to residue 40.

20. The NANBV structural protein of claim 19 wherein said protein includes an amino acid residue sequence contained in SEQ. ID NO. 6 from residue 1 to residue 271.

21. A composition comprising the NANBV structural protein of claim 15, 17 or 19.

22. A diagnostic system, in kit form, for assaying a body fluid sample for the presence of antibodies against NANBV structural antigens comprising, in an amount sufficient to perform at least one assay, a NANBV structural protein according to claim 15.

23. The diagnostic system according to claim 22 wherein said NANBV structural protein is affixed to a solid matrix and has an amino acid residue sequence represented by SEQ. ID NO. 3 from residue 1 to residue 252.

24. A diagnostic system, in kit form, for assaying a body fluid sample for the presence of antibodies against NANBV structural antigens comprising, in an amount sufficient to perform at least one assay, a NANBV structural protein according to claim 17.

25. The diagnostic system according to claim 24 wherein said NANBV structural protein is affixed to a solid matrix and has an amino acid residue sequence represented by SEQ. ID NO. 4 from residue 1 to residue 252.

26. A diagnostic system, in kit form, for assaying a body fluid sample for the presence of antibodies against NANBV structural antigens comprising, in an amount sufficient to perform at least one assay, a NANBV structural protein according to claim 19.

27. The diagnostic system according to claim 26 wherein said NANBV structural protein is affixed to a solid matrix and has an amino acid residue sequence represented by SEQ. ID NO. 6 from residue 1 to residue 271.

28. A diagnostic system, in kit form, for assaying a body fluid sample for the presence of NANBV structural antigens comprising, in an amount sufficient to perform at least one assay, an anti-NANBV structural protein antibody,

said antibody having the capacity to immunoreact with a NANBV structural protein according to claim 15.

29. The diagnostic system of claim 28 that further includes, in an amount sufficient to perform at least one assay, a labeled NANBV structural protein according to claim 15.

30. A diagnostic system, in kit form, for assaying a body fluid sample for the presence of NANBV structural antigens comprising, in an amount sufficient to perform at least one assay, an anti-NANBV structural protein antibody, said antibody having the capacity to immunoreact with a NANBV structural protein according to claim 17.

31. The diagnostic system of claim 30 that further includes, in an amount sufficient to perform at least one assay, a labeled NANBV structural protein according to claim 17.

32. A diagnostic system, in kit form, for assaying a body fluid sample for the presence of NANBV structural antigens comprising, in an amount sufficient to perform at least one assay, an anti-NANBV structural protein antibody, said antibody having the capacity to immunoreact with a NANBV structural protein according to claim 19.

33. The diagnostic system of claim 32 that further includes, in an amount sufficient to perform at least one assay, a labeled NANBV structural protein according to claim 19.

34. The diagnostic system of claim 28, 30, or 32 wherein said antibody is affixed to a solid matrix.

35. A method of assaying a body fluid sample for the presence of antibodies against a NANBV structural antigen, which method comprises:

a) forming an immunoreaction admixture by admixing said body fluid sample with a NANBV structural protein, said protein including an amino acid residue sequence represented by the sequence contained in SEQ. ID NO. 1 from residue 1 to

1-74 residue 20, from residue 21 to residue 40, or from residue 2
 69-126 to residue 40;

121-176 b) maintaining said immunoreaction admixture for a time
 period sufficient for any of said antibodies present to
 5 immunoreact with said NANBV structural protein to form an
 immunoreaction product; and

c) detecting the presence of any of said immunoreaction
 product formed and thereby the presence of said antibodies.

36. The method of claim 35 wherein said NANBV structural
 10 protein has an amino acid residue sequence contained in SEQ.

ID NO. 3 from residue 1 to residue 252.

37. The method of claim 36 wherein said NANBV structural
 protein has an amino acid residue sequence contained in SEQ.

ID NO. 4 from residue 1 to residue 252.

15 38. The method of claim 37 wherein said NANBV structural
 protein has an amino acid residue sequence contained in SEQ.
 ID NO. 6 from residue 1 to residue 271.

39. The method of claim 35 wherein said NANBV structural
 protein is affixed to a solid matrix.

20 40. The method of claim 39 wherein said detecting in
 step (c) comprises the steps of:

(i) admixing said immunoreaction product formed in
 step (c) with a labeled specific binding agent to form a
 labeling admixture, said labeled specific binding agent
 25 comprising a specific binding agent and a label;

(ii) maintaining said labeling admixture for a time
 period sufficient for any of said immunoreaction product
 present to bind with said labeled specific binding agent to
 form a labeled product; and

30 (iii) detecting the presence of any of said labeled
 product formed, and thereby the presence of said
 immunoreaction product.

41. The method of claim 40 wherein said specific binding
 agent is Protein A.

42. The method of claim 40 wherein said specific binding agent is at least one of the antibodies anti-human IgG and anti-human IgM.

43. The method of claim 40 wherein said label is lanthanide chelate.

44. The method of claim 40 wherein said label is biotin.

45. The method of claim 40 wherein said label is an enzyme.

46. The method of claim 40 wherein said label is a radioactive isotope.

47. A vaccine comprising an immunologically effective amount of a NANBV structural protein according to claim 15 in a pharmaceutically acceptable carrier.

48. The vaccine of claim 47 wherein said NANBV structural protein has an amino acid residue sequence represented by SEQ. ID NO. 3 from residue 225 to residue 252.

49. A vaccine comprising an immunologically effective amount of a NANBV structural protein according to claim 17 in a pharmaceutically acceptable carrier.

50. The vaccine of claim 49 wherein said NANBV structural protein has an amino acid residue sequence represented by SEQ. ID NO. 4 from residue 225 to residue 252.

51. A vaccine comprising an immunologically effective amount of a NANBV structural protein according to claim 19 in a pharmaceutically acceptable carrier.

52. The vaccine of claim 51 wherein said NANBV structural protein has an amino acid residue sequence represented by SEQ. ID NO. 6 from residue 225 to residue 271.

53. A method for inducing immunity to NANBV infection comprising administering an inoculum comprising an immunologically effective amount of the NANBV structural protein according to claim 15, 17 or 19, in a pharmaceutically acceptable carrier.

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PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

I HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated next to my name in PART A on page 2 hereof.

I believe I am the original, first, and sole inventor (if only one name is listed) or an original, first, and joint inventor (if plural names are listed) of the subject matter which is claimed and for which a patent is sought on the invention entitled NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES

the specification of which:

☒ is attached hereto
☐ was filed on _____ as Application Serial No. _____
and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate listed in PART B on page 2 hereof and have also identified in PART B on page 2 hereof any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed in PART C on page 2 hereof and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Sec. 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following as my attorneys or agents with full power of substitution to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

Douglas A. Bingham	Reg. No. 32,457	Talivaldis Cepuritis	Reg. No. 20,818	Ernest Cheslow	Reg. No. 17,019
Max Dressler	Reg. No. 14,123	William C. Fuess	Reg. No. 30,054	Edward P. Gamson	Reg. No. 29,381
Stephen D. Geimer	Reg. No. 28,846	John W. Harbst	Reg. No. 28,018	Allen J. Hoover	Reg. No. 24,103
Henry S. Kaplan	Reg. No. 25,346	Martin L. Katz	Reg. No. 25,011	John W. Klooster	Reg. No. 18,953
Gerson E. Meyers	Reg. No. 21,160	John P. Milnamow	Reg. No. 20,635	Paul M. Odell	Reg. No. 28,332
Jack Shore	Reg. No. 17,551	Joel E. Siegel	Reg. No. 25,440	Joseph M. Sorrentino	Reg. No. 32,598
Steven J. Soucar	Reg. No. 32,440	John P. Sumner	Reg. No. 33,039	Marshall W. Sutker	Reg. No. 19,962
Paul M. Vargo	Reg. No. 29,116	Lois P. Besanko	Reg. No. 27,855	Thomas Fitting	Reg. No. 34,163

whose mailing address for this application is DRESSLER, GOLDSMITH, SHORE, SUTKER & MILNAMOW, LTD.
11300 Sorrento Valley Road, Suite 200
San Diego, California 92121
Telephone: (619) 546-1555

See Page 2 attached, signed, and made a part hereof.

"EXPRESS MAIL" LABEL NO. 88 18770 39

Page 2 of 2
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PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

PART A: Inventor Information And Signature

Full name of SOLE or FIRST inventor 40100 et al
Citizenship USA Residence Suzanne Zebedee
7544 Charmant Drive
San Diego, CA 92122
Post Office Address (If different) _____

Inventor's signature: _____ Date: _____

Full name of SECOND joint inventor, if any Genevieve Inchauspe
Citizenship France Residence 504 East 63rd Street
New York, NY 10021
Post Office Address (If different) _____

Second Inventor's signature: _____ Date: _____

Full name of THIRD joint inventor, if any Marc S Nagoff
Citizenship USA Residence 11734 Mira Lago Way
San Diego, CA 92131
Post Office Address (If different) _____

Third Inventor's signature: _____ Date: _____

Full name of FOURTH joint inventor, if any Alfred M. Prince
Citizenship USA Residence 154 Stone Gill Road, Pound Ridge
New York, NY 10576
Post Office Address (If different) _____

Fourth Inventor's signature: _____ Date: _____

Full name of FIFTH joint inventor, if any _____
Citizenship _____ Residence _____
Post Office Address (If different) _____

Fifth Inventor's signature: _____ Date: _____

PART B: Prior Foreign Application(s)

Serial No.	Country	Day/Month/Year Filed	Priority Claimed
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

PART C: Claim For Benefit Of Filing Date Of Earlier U.S. Application(s)

Serial No.	Filing Date	Status:
07/573,643	August 25, 1990	<input type="checkbox"/> Patented <input checked="" type="checkbox"/> Pending <input type="checkbox"/> Abandoned
		<input type="checkbox"/> Patented <input type="checkbox"/> Pending <input type="checkbox"/> Abandoned

See Page 1 to which this is attached and from which this Page 2 continues.



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PATENT

TRANSMITTAL OF UTILITY PATENT APPLICATION FOR FILING

Certification under 37 CFR 1.10 (if applicable)

RB187707729

"Express Mail" mailing label number

11/21/90

Date of deposit

I hereby certify that this Transmittal letter, enclosed application, and any other documents referred to as enclosed herein are being deposited in an envelope with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Alice M. Fraga
(Typed or printed name of person mailing application)

Alice M. Fraga
(Signature of person mailing application)

COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the utility patent application of inventor(s): Suzanne Zebedee, Genevieve Inchausti, Marc S. Nasoff, Alfred M. Prince and entitled: NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES

1. Enclosed are:

- ☒ A duplicate copy of this transmittal letter.
☒ One stamped, self-addressed postcard for the PTO Mail Room date stamp.
☒ One utility patent application containing pages 1 - 96, and
☒ a declaration or oath for the utility patent application including a power of attorney, and
☐ drawings: ☐ 1 copy of _____ sheets of formal drawings, OR
☐ 1 copy of _____ sheets of informal drawings, OR
☐ 1 set of _____ Bristol board sheets of original, formal drawings.
☐ A certified copy of a _____ application, No. _____.
☐ An associate power of attorney.
☐ An Information Disclosure Statement.
☐ Verified Statement(s) relating to small entity status.
☐ Other: _____

2. The filing fee has been calculated as shown below:

	(Col. 1)	(Col. 2)
FOR:	NO. FILED	NO. EXTRA
BASIC FEE		
TOTAL CLAIMS	53 - 20	* 33
INDEP. CLAIMS	23 - 3	* 20
<input checked="" type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENTED		

* If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

SMALL ENTITY	
RATE	FEE
	\$ 315
x \$ 6 =	\$
x \$ 18 =	\$
+ \$ 60 =	\$
TOTAL	\$

CR
CR
CR
CR
CR

OTHER THAN A SMALL ENTITY	
RATE	FEE
	\$ 630
x \$ 12 =	\$ 396
x \$ 36 =	\$ 720
+ \$ 120 =	\$ 120
TOTAL	\$ 1866

- ☐ Please charge my Deposit Account No. 04-1644 in the amount of \$ _____.
☒ A check in the amount of \$ 1866.00 to cover the filing fee is enclosed.
☒ The Commissioner is authorized to charge payment of the following amounts associated with this communication or credit any overpayment to Deposit Account No. 04-1644:
☒ Additional filing fees under 37 CFR 1.16 or deficiencies in remittances therefor.
☒ Additional processing fees under 37 CFR 1.17 or deficiencies in remittances therefor.
☒ Any deficiency in any patent issue fee under 37 CFR 1.18 for which partial payment is made.

3. The enclosed utility patent application is related to 07/573,643 filed August 25, 1990Date: November 21, 1990Attorney's Signature Thomas Pitting
Name and Reg. No. Thomas Pitting, 34, 163

Correspondence Address:

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Suzanne Zebedee
07/616,369
November 21, 1990

MAILED

DEC 31 1990

APPLICATION BRANCH

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS
CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE
DISCLOSURES**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR §§ 1.821 through 1.825 as follows:

- #2
- ☐ 1. This application clearly fails to comply with the collective requirements of §§ 1.821 through 1.825. Applicant's attention is directed to these regulations, a copy of which is attached.
- ☐ 2. This application does not conform exclusively to the requirements of §§ 1.821 through 1.825. The non-conforming material should be deleted. § 1.821(b).
- ☐ 3. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing." § 1.821(c).
- ☐ 4. This application does contain, as a separate part of the disclosure on paper copy, a "Sequence Listing." However, the "Sequence Listing" does not comply with the requirements of §§ 1.821 through 1.825 as follows:
- ☐ a. The sequence data does not comply with the symbol and format requirements of paragraphs (b) through (p) of § 1.822. Specifically: _____
- ☐ b. The "Sequence Listing" does not comply with the location and page requirements of paragraph (a) of § 1.823.
- ☐ c. The "Sequence Listing" does not comply with the information requirements of paragraph (b) of § 1.823. Specifically: _____
- ☐ d. Other: _____
- ☐ 5. The description and/or claims of the patent application mention a sequence that is set forth in the "Sequence Listing" but reference is not properly made to the sequence by use of a sequence identifier as required by § 1.821(d).
- ☒ 6. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by § 1.821(e).
- ☐ 7. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the computer readable form does not comply with the requirements of § 1.824. Specifically: _____
- ☐ 8. A statement that the content of the paper and computer readable copies are the same has not been submitted as required by § 1.821(f).
- ☐ 9. The amendment to or replacement of the paper and/or computer readable copies of the "Sequence Listing" does not comply with the requirements of § 1.825(a) through (c).
- ☐ 10. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable. Applicant must provide a substitute copy of the data in computer readable form accompanied by a statement that the substitute data is identical to that originally filed. § 1.825(d). Specifically: _____
- ☐ 11. Other: _____

APPLICANT IS GIVEN ONE MONTH FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE ABOVE REQUIREMENTS. Failure to comply with the above requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136. Direct the response to, and any questions about, this notice to the undersigned. A copy of this notice MUST be returned with your response.

Dora Straub
For: Manager, Application Processing Division

☐ Examining Group _____



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER FILING DATE FIRST NAMED APPLICANT ATTY DOCKET NO./TITLE

07/616,369 11/21/90 ZEBEDEE

S PHA0026

DRESSLER, GOLDSMITH, SHORE,
SUTKER & MILNAMOW, LTD.
11300 SORRENTO VALLEY RD, STE 200
SAN DIEGO, CA 92121

000

DATE MAILED: 12/31/90

NOTICE TO FILE MISSING PARTS OF APPLICATION
FILING DATE GRANTED

A filing date has been granted to this application. However, the following parts are missing.

If all missing parts are filed within the period set below, the total amount owed by applicant as a

☒ large entity, ☐ small entity (verified statement filed), is \$ 404.00

1. ☐ The statutory basic filing fee is: ☐ missing ☐ insufficient. Applicant as a ☐ large entity
☐ small entity, must submit \$ _____ to complete the basic filing fee and MUST ALSO
SUBMIT THE SURCHARGE AS INDICATED BELOW.

2. ☒ Additional claim fees of \$ 284.00 as a ☒ large entity ☐ small entity, including any required multiple
dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional
claims for which fees are due. NO SURCHARGE IS REQUIRED FOR THIS ITEM.

3. ☐ The oath or declaration:
☐ is missing.
☐ does not cover items omitted at time of execution.

An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application
Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED
BELOW.

4. ☐ The oath or declaration does not identify the application to which it applies. An oath or declaration in
compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date
is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.

5. ☒ The signature to the oath or declaration is: ☒ missing; ☐ a reproduction; ☐ by a person other than the
inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in
compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date
is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW..

6. ☐ The signature of the following joint inventor(s) is missing from the oath or declaration:

_____. An oath or declaration listing the names of all inventors and signed by
the omitted inventor(s), identifying this application by the above Application Number and Receipt Date is
required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.

7. ☐ The application was filed in a language other than English. Applicant must file a verified English
translation of the application and a fee of \$30.00 under 37 CFR 1.17(k), unless this fee has already been
paid. NO SURCHARGE IS REQUIRED FOR THIS ITEM.

8. ☐ A \$50.00 processing fee is required for returned checks. (37 CFR 1.21(m)).

9. ☐ Your filing receipt was mailed in error because check was returned without payment.

10. ☐ Other.

An Application Number and Filing Date have been assigned to this application. The missing parts and fees
identified above in items 1 and 3-6 must be timely provided ALONG WITH THE PAYMENT OF A
SURCHARGE of \$120.00 for large entities or \$60.00 for small entities who have filed a verified statement
claiming such status. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given ONE MONTH FROM
THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application,
WHICHEVER IS LATER, within which to file all missing parts and pay any fees required above to avoid
abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee
under the provisions of 37 CFR 1.136(a).

Direct the response to, and any questions about, this notice to ATTENTION: Application Division,
Special Handling Unit.

Dora Shaw
A copy of this notice **MUST** be returned with response.

For: Manager, Application Division

(703) 557-308-1203



030 12/31/90 100-115 #4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Zebedee et al.)
SERIAL NO.: 07/616,369) GROUP ART UNIT: Unassigned
FILED: November 21, 1990) EXAMINER: Unassigned
FOR: NON-A, NON-B HEPATITIS)
VIRUS ANTIGEN, DIAGNOSTIC)
METHODS AND VACCINES) San Diego, California
Ref. No. PHA0026P

PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. §1.136(a)

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

A one-month Extension of Time is requested for filing of the response to the Notice to File Missing Parts, mailed December 31, 1990.

Enclosed is check # 3571 in the amount of \$100.00 to cover the charge set forth in 37 C.F.R. 1.17 (a).

Please charge any additional fee concerning this matter to our Deposit Account No. 04-1644.

Respectfully submitted,

By Thomas Fitting
Thomas Fitting, Reg. No. 34,163

DRESSLER, GOLDSMITH, SHORE, SUTKER & MILNAMOW, LTD.
11300 Sorrento Valley Road, Suite 200
San Diego, California 92121
619/546-1555

RECEIVED

MAR 4 1991

CERTIFICATE OF MAILING

I hereby certify that this PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. §1.136(a) is being deposited on the date indicated below with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington DC 20231.

Thomas Fitting
Thomas Fitting
120 LA 03/01/91 07616369

22 February 1991
Date

1 115 100.00 CK

#3



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Zebedee et al.)	
Serial No.:	07/616,369)	Group Art Unit
Filed:	November 21, 1990)	Unassigned
For:	NON-A, NON-B HEPATITIS VIRUS)	Examiner:
	ANTIGEN, DIAGNOSTIC METHODS)	Unassigned
	AND VACCINES)	

PHA0026P
San Diego, California

COMMUNICATION

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Notice of Missing Parts of Application Under 37 C.F.R. §1.53(d) of December 31, 1990, enclosed is a Declaration signed by applicant that refers to the above application.

Enclosed is Check # 3572 in the amount of \$120.00 to cover the surcharge set forth in 37 C.F.R. §1.16(e).

Also enclosed is Check # 3573 in the amount of \$284.00 to cover the additional claim fees.

Please charge any additional fee concerning this matter to our Deposit Account No. 04-1644.

Respectfully submitted,

By Thomas Fitting
Thomas Fitting, Reg. No. 34,163

DRESSLER, GOLDSMITH, SHORE,
SUTKER & MILNAMOW, LTD.
11300 Sorrento Valley Road, Suite 200
San Diego, California 92121
(619)546-1555

CERTIFICATE OF MAILING

I hereby certify that this COMMUNICATION is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Thomas Fitting
Thomas Fitting

22 Feb 1991
Date of Deposit

PPRESS MAIL LABEL NO. 18770772

PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated next to my name in PART A on page 2 hereof.

I believe I am the original, first, and sole inventor (if only one name is listed) or an original, first, and joint inventor (if plural names are listed) of the subject matter which is claimed and for which a patent is sought on the invention entitled NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES

the specification of which:

- ☐ is attached hereto
☒ was filed on November 21, 1990 as Application Serial No. 07/616,369
and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate listed in PART B on page 2 hereof and have also identified in PART B on page 2 hereof any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed in PART C on page 2 hereof and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Sec. 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following as my attorneys or agents with full power of substitution to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

Douglas A. Bingham	Reg. No. <u>32,457</u>	Talivaldis Cepuritis	Reg. No. <u>20,818</u>	Ernest Cheslow	Reg. No. <u>17,019</u>
Max Dressler	Reg. No. <u>14,123</u>	William C. Fuess	Reg. No. <u>30,054</u>	Edward P. Ganson	Reg. No. <u>29,381</u>
Stephen D. Geimer	Reg. No. <u>28,846</u>	John W. Harbst	Reg. No. <u>28,018</u>	Allen J. Hoover	Reg. No. <u>24,103</u>
Henry S. Kaplan	Reg. No. <u>25,346</u>	Martin L. Katz	Reg. No. <u>25,011</u>	John W. Klooster	Reg. No. <u>18,953</u>
Gerson E. Meyers	Reg. No. <u>21,160</u>	John P. Milnamow	Reg. No. <u>20,635</u>	Paul M. Odell	Reg. No. <u>28,332</u>
Jack Shore	Reg. No. <u>17,551</u>	Joel E. Siegel	Reg. No. <u>25,440</u>	Joseph M. Sorrentino	Reg. No. <u>32,598</u>
Sтивен J. Soucar	Reg. No. <u>32,440</u>	John P. Sumner	Reg. No. <u>33,039</u>	Marshall W. Suter	Reg. No. <u>19,962</u>
Paul M. Vargo	Reg. No. <u>29,116</u>	Lois P. Besanko	Reg. No. <u>27,855</u>	Thomas Fitting	Reg. No. <u>34,163</u>

whose mailing address for this application is 602 DRESSLER, GOLDSMITH, SHORE, SUTHER & MILNAMOW, LTD.
701 11300 Sorrento Valley Road, Suite 200
San Diego, California 92121
Telephone: (619) 546-1555

See Page 2 attached, signed, and made a part hereof.

EXPRESS MAIL LABEL NO. 187707



PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

PART A: Inventor Information And Signature 40100
Full name of SOLE or FIRST Inventor Suzanne Zebedee
Citizenship USA Residence 7544 Charmant Drive
San Diego, CA 92122
Post Office Address (If different) _____

Inventor's signature: Suzanne Zebedee Date: Feb 12, 1991

Full name of SECOND joint Inventor, If any Genevieve Inchauspe
Citizenship France Residence 504 East 63rd Street
New York, NY 10021
Post Office Address (If different) _____

Second Inventor's signature: _____ Date: _____

Full name of THIRD joint Inventor, If any 40300
Marc S Nasoff
Citizenship USA Residence 11734 Mira Lago Way
San Diego, CA 92131
Post Office Address (If different) _____

Third Inventor's signature: Marc S Nasoff Date: Feb. 12, 1991

Full name of FOURTH joint Inventor, If any Alfred M. Prince
Citizenship USA Residence 154 Stone Gill Road, Pound Ridge
New York, NY 10576
Post Office Address (If different) _____

Fourth Inventor's signature: _____ Date: _____

Full name of FIFTH joint Inventor, If any _____
Citizenship _____ Residence _____
Post Office Address (If different) _____

Fifth Inventor's signature: _____ Date: _____

PART B: Prior Foreign Application(s)

Serial No.	Country	Day/Month/Year Filed	Priority Claimed
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

PART C: Claim For Benefit Of Filing Date Of Earlier U.S. Application(s)

Serial No.	Filing Date	Status:
07/573,643	August 25, 1990	<input type="checkbox"/> Patented <input checked="" type="checkbox"/> Pending <input type="checkbox"/> Abandoned
		<input type="checkbox"/> Patented <input type="checkbox"/> Pending <input type="checkbox"/> Abandoned

See Page 1 to which this is attached and from which this Page 2 continues.

EXPRESS MAIL LABEL NO. 1877077

Page 1 of 2
PBA0026



PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

I HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated next to my name in PART A on page 2 hereof.

I believe I am the original, first, and sole inventor (if only one name is listed) or an original, first, and joint inventor (if plural names are listed) of the subject matter which is claimed and for which a patent is sought on the invention entitled NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES

the specification of which:

- ☐ is attached hereto
☒ was filed on November 21, 1990 as Application Serial No. 07/616,369
and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate listed in PART B on page 2 hereof and have also identified in PART B on page 2 hereof any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed in PART C on page 2 hereof and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Sec. 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following as my attorneys or agents with full power of substitution to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

Douglas A. Bingham	Reg. No. 32,457	Talivaldis Cepuritis	Reg. No. 20,818	Ernest Cheslow	Reg. No. 17,019
Max Dressler	Reg. No. 14,123	William C. Fuess	Reg. No. 30,054	Edward P. Ganson	Reg. No. 29,381
Stephen D. Geimer	Reg. No. 28,846	John W. Harbst	Reg. No. 28,018	Allen J. Hoover	Reg. No. 24,169
Henry S. Kaplan	Reg. No. 25,346	Martin L. Katz	Reg. No. 25,011	John W. Klooster	Reg. No. 18,953
Gerson E. Meyers	Reg. No. 21,160	John P. Milnamow	Reg. No. 20,635	Paul M. Odell	Reg. No. 28,332
Jack Shore	Reg. No. 17,551	Joel E. Siegel	Reg. No. 25,440	Joseph M. Sorrentino	Reg. No. 32,598
Steven J. Soucar	Reg. No. 32,440	John P. Sumner	Reg. No. 33,039	Marshall W. Sutker	Reg. No. 19,962
Paul M. Vargo	Reg. No. 29,116	Lois P. Besanko	Reg. No. 27,855	Thomas Fitting	Reg. No. 34,163

whose mailing address for this application is: DRESSLER, GOLDSMITH, SHORE, SUTKER & MILNAMOW, LTD.
11300 Solanco Valley Road, Suite 200
San Diego, California 92121
Telephone: (619) 546-1555

See Page 2 attached, signed, and made a part hereof.

EXPRESS MAIL LABEL NO. 88 1877077

Page 2 of 2
PHA0026



PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

PART A: Inventor Information And Signature

Full name of SOLE or FIRST inventor Suzanne Zebedee
Citizenship USA Residence 7544 Charmant Drive
San Diego, CA 92122
Post Office Address (If different) _____

Inventor's signature: _____ Date: _____

Full name of SECOND joint inventor, if any Genevieve Inchauspe
Citizenship France Residence 504 East 63rd Street
New York, NY 10021
Post Office Address (If different) _____

Second Inventor's signature: Genevieve Inchauspe Date: 1-28-91

Full name of THIRD joint inventor, if any Marc S Nasoff
Citizenship USA Residence 11734 Mira Lago Way
San Diego, CA 92131
Post Office Address (If different) _____

Third Inventor's signature: _____ Date: _____

Full name of FOURTH joint inventor, if any Alfred M. Prince
Citizenship USA Residence 154 Stone Gill Road, Pound Ridge
New York, NY 10576
Post Office Address (If different) _____

Fourth Inventor's signature: Alfred M. Prince Date: 1-27-91

Full name of FIFTH joint inventor, if any _____
Citizenship _____ Residence _____
Post Office Address (If different) _____

Fifth Inventor's signature: _____ Date: _____

PART B: Prior Foreign Application(s)

Serial No. _____ Country _____

Day/Month/Year Filed _____

Priority Claimed
☐ Yes ☐ No
☐ Yes ☐ No

PART C: Claim For Benefit Of Filing Date Of Earlier U.S. Application(s)

Serial No. _____ Filing Date _____
07/573,643 August 25, 1990

Status:
☐ Patented ☒ Pending ☐ Abandoned
☐ Patented ☐ Pending ☐ Abandoned

See Page 1 to which this is attached and from which this Page 2 continues.



120-105-#
284-102-5 A/N

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO./TITLE
07/616,369	11/21/90	ZEBEDEE	6 PHA0026

DRESSLER, GOLDSMITH, SHORE,
SUTKER & NILNAMOW, LTD.
11300 SORRENTO VALLEY RD., STE 200
SAN DIEGO, CA 92121

000

DATE MAILED: 12/31/90

**NOTICE TO FILE MISSING PARTS OF APPLICATION
FILING DATE GRANTED**

A filing date has been granted to this application. However, the following parts are missing.

If all missing parts are filed within the period set below, the total amount owed by applicant as a

☒ large entity, ☐ small entity (verified statement filed), is \$ 404.00

1. ☐ The statutory basic filing fee is: ☐ missing ☐ insufficient. Applicant as a ☐ large entity
☐ small entity, must submit \$ _____ to complete the basic filing fee and MUST ALSO
SUBMIT THE SURCHARGE AS INDICATED BELOW.
2. ☒ Additional claim fees of \$ 284.00 as a ☒ large entity ☐ small entity, including any required multiple
dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional
claims for which fees are due. NO SURCHARGE IS REQUIRED FOR THIS ITEM.
3. ☐ The oath or declaration:
☐ is missing.
☐ does not cover items omitted at time of execution.
An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application
Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED
BELOW.
4. ☐ The oath or declaration does not identify the application to which it applies. An oath or declaration in
compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date
is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
5. ☒ The signature to the oath or declaration is: ☒ missing; ☐ a reproduction; ☐ by a person other than the
inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in
compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date
is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
6. ☐ The signature of the following joint inventor(s) is missing from the oath or declaration:
_____. An oath or declaration listing the names of all inventors and signed by
the omitted inventor(s), identifying this application by the above Application Number and Receipt Date is
required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
7. ☐ The application was filed in a language other than English. Applicant must file a verified English
translation of the application and a fee of \$30.00 under 37 CFR 1.17(k), unless this fee has already been
paid. NO SURCHARGE IS REQUIRED FOR THIS ITEM.
8. ☐ A \$50.00 processing fee is required for returned checks. (37 CFR 1.21(m)).
9. ☐ Your filing receipt was mailed in error because check was returned without payment.
10. ☐ Other.

An Application Number and Filing Date have been assigned to this application. The missing parts and fees
identified above in items 1 and 3-6 must be timely provided ALONG WITH THE PAYMENT OF A
SURCHARGE of \$120.00 for large entities or \$60.00 for small entities who have filed a verified statement
claiming such status. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given ONE MONTH FROM
THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application,
WHICHEVER IS LATER, within which to file all missing parts and pay any fees required above to avoid
abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee
under the provisions of 37 CFR 1.136(a).

Direct the response to the Commissioner of Patents and Trademarks about this notice to ATTENTION: Application Division,
Special Handling Unit.

Dora Strunk
A copy of this notice MUST be returned with response.

For: Manager, Application Division
(703) 557-308-1203

120 LA 03/01/91 070-4365

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#6/A

Applicant: Zebedee et al.)
Serial No.: 07/616,369) Group Art Unit:
Filed: November 21, 1990) Unassigned
For: NON-A, NON-B HEPATITIS VIRUS) Examiner: Unassigned
ANTIGENS, DIAGNOSTIC METHODS)
AND VACCINES) Our Ref. No. PHA 0026P
San Diego, California

PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to the examination of the merits, please amend the above-identified application to comply with the requirements under 37 CFR §1.821(d) for referring to sequences in a patent application by use of sequence identifiers as follows:

IN THE SPECIFICATION

At page 48, line 25, insert "and consecutive SEQ ID NOs beginning with 15 and ending with 23" between "sequences" and "as".

At page 56, line 33, insert "(SEQ ID NO 25)" between "sequence" and ":".

At page 56, line 35, insert "(SEQ ID NO 24)" between "sequence" and ":".

At page 57, line 6, insert "(SEQ ID NO 27)" between "sequence" and ":".

At page 57, line 8, insert "(SEQ ID NO 26)" between "sequence" and ":".

At page 58, line 2, insert "(SEQ ID NO 29)" between "sequence" and ":".

At page 58, line 4, insert "(SEQ ID NO 28)" between "sequence" and ":".

At page 58, line 12, insert "(SEQ ID NO 31)" between "sequence" and ":".

At page 58, line 14, insert "(SEQ ID NO 30)" between "sequence" and ":".

At page 59, line 8, insert "(SEQ ID NO 33)" between "sequence" and ":".

At page 59, line 10, insert "(SEQ ID NO 32)" between "sequence" and ":".

At page 59, line 17, insert "(SEQ ID NO 35)" between "sequence" and ":".

At page 59, line 19, insert "(SEQ ID NO 34)" between "sequence" and ":".

At page 60, line 12, insert "(SEQ ID NO 37)" between "sequence" and ":".

At page 60, line 14, insert "(SEQ ID NO 36)" between "sequence" and ":".

At page 60, line 17, insert "(SEQ ID NO 39)" between "sequence" and ":".

At page 60, line 19, insert "(SEQ ID NO 38)" between "sequence" and ":".

At page 60, line 25, insert "(SEQ ID NO 41)" between "sequence" and ":".

At page 60, line 27, insert "(SEQ ID NO 40)" after "sequence".

At page 61, line 32, insert "(SEQ ID NO 43)" between "sequence" and ":".

At page 61, line 34, insert "(SEQ ID NO 42)" between "sequence" and ":".

At page 62, line 5, insert "(SEQ ID NO 45)" between "sequence" and ":".

At page 62, line 7, insert "(SEQ ID NO 44)" between "sequence" and ":".

At page 90 through 96, delete the original page numbers and renumber them consecutively beginning with 118 and ending with 124 to adjust for the insertion of the amended Sequence Listing beginning at new page 90 and ending at new page 117, after the original incomplete Sequence Listing and before the Claims.

At page 59, line 9, delete the two amino acid residues represented by the three-letter code "Leu Arg" and replace with the two amino acid residues represented by the three-letter code "Ser Cys".

At page 60, line 18, delete the two amino acid residues represented by the three-letter code "Leu Arg" and replace with the two amino acid residues represented by the three-letter code "Ser Cys".

REMARKS

The amendments to the specification are to insert Sequence Listing identifiers (SEQ ID NO) adjacent to descriptions to nucleotide and/or amino acid sequences in the specification corresponding to their designation in the amended Sequence Listing.

Support for the amendments to the specification inserting SEQ ID NO can be found by referring to the disclosed sequences one line below each individual amendment.

The amendments to the specification on pages 59 and 60 for replacing the amino acid residues, Leu and Arg, with Ser and Cys, respectively, are made to correct a typographical error. It is well known in the art that the triplet nucleotide codons, TCC and TGC, encode the respective amino acid residues, Ser and Cys. The incorrect amino acid residues were mistakenly designated. The correct designations can be found in the specification. For example, the correct translation for TCC can be found by referring to SEQ ID NO 1 on page 79, line 33, wherein the triplet codon

Serial No. 07/616,369

- 4 -

nucleotide base sequence TCC at base positions 156-158 encodes the amino acid residue Serine (Ser) and not Leucine (Leu) at amino acid residue position 53 on line 34 below triplet codon TCC. An example of the correct translation for TGC can be found by referring to SEQ ID NO 1 on page 80, line 2, wherein the triplet codon nucleotide base sequence TGC at base positions 271-273 encodes the amino acid residue Cysteine (Cys) and not Arginine (Arg) at amino acid position 91 on line 3 below trip codon TGC.

Applicants maintain that no new matter is presented by the amendments to the specification, and respectfully request entry of these amendments.

Respectfully submitted,

By Thomas Fitting
Thomas Fitting, Reg. No. 34,163

DRESSLER, GOLDSMITH, SHORE, SUTKER & MILNAMOW, LTD.
11300 Sorrento Valley Road, Suite 200
San Diego, California 92121
(619) 546-1555

CERTIFICATE OF MAILING

I hereby certify that this PRELIMINARY AMENDMENT is being deposited on the date indicated below with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Box Sequence, Washington, D.C. 20231.

Thomas Fitting
Thomas Fitting, Reg. No. 34,163

May 31, 1991
Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 07/616,369) Group Art Unit:
Filed: November 21, 1990) Unassigned
For: NON-A, NON-B HEPATITIS VIRUS) Examiner: Unassigned
ANTIGENS, DIAGNOSTIC METHODS)
AND VACCINES) Our Ref. No. PHA 0026P
San Diego, California)

PETITION FOR EXTENSION OF TIME UNDER 37 CFR §1.136(a)

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

A four-month Extension of Time is requested for filing of the response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, mailed December 31, 1990.

Enclosed is Check No. 3683 in the amount of \$1,150.00 to cover the charge set forth in 37 CFR §1.17(a).

Please charge any additional fee concerning this matter to our Deposit Account No. 04-1644.

Respectfully Submitted,

By: Thomas Fitting
Thomas Fitting, Reg. No. 34,163

DRESSLER, GOLDSMITH, SHORE, SUTKER & MILNAMOW, LTD.
11300 Sorrento Valley Road, Suite 200
San Diego, California 92121
(619) 546-1555

CERTIFICATE OF MAILING

I hereby certify that this PETITION FOR EXTENSION OF TIME UNDER 37 CFR §1.136(a) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date written below.

Thomas Fitting May 31, 1991
Thomas Fitting Date of Deposit

#6
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date indicated below with sufficient postage as First Class Mail in an envelope addressed to: Honorable Commissioner of Patents and Trademarks, Box Sequence, Washington, D.C. 20231, Attn: Dora Stroud, Application Processing Division.

Thomas Fitting
Thomas Fitting, Reg. No. 32,457

May 31, 1991
Date of Deposit

Applicant: Zebedee et al.)	
Serial No.: 07/616,369)	Group Art Unit:
Filed: November 21, 1990)	Unassigned
For: NON-A, NON-B HEPATITIS VIRUS)	Examiner: Unassigned
ANTIGENS, DIAGNOSTIC METHODS)	
AND VACCINES)	Our Ref. No. PHA 0026P
)	San Diego, California

RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT
APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO
ACID SEQUENCE DISCLOSURES (37 C.F.R. 1.821-1.825)

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231
Attn: Dora Stroud
Application Processing Division

Dear Sir:

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures Under 37 C.F.R. §1.821-1.825 mailed December 31, 1991, enclosed is an amended Sequence Listing on paper copy, made in accordance with 37 CFR §1.821(a). Also enclosed is a copy of the Sequence Listing in computer readable form, submitted as required by 37 CFR §1.821(e), on which the Sequence Listing is labeled PHA0026S.APP.

An amended Sequence Listing is submitted although not formally requested on the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. The Sequence Listing submitted with

the application was a partial listing containing sequences corresponding to SEQ ID NOs 1-14. Additional sequences disclosed in the specification corresponding to SEQ ID NOs 15-45 were not specifically listed in the Sequence Listing. The enclosed paper copy of the amended Sequence Listing contains all 45 sequences, including the original 14 sequences.

Also enclosed is a Preliminary Amendment in which amendments to the specification have been made in order to comply with 37 CFR §1.821(d).

I hereby state that the amendments, made in accordance with 37 CFR §1.825(a) through (c), which are submitted in the amended Sequence Listing, are supported by the application as filed at pages 48, 49, 56-62, and 76-89. I hereby state that the amended Sequence Listing does not include new matter.

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted in accordance with 37 CFR §1.821(a) through (c) and (e), respectively, are the same.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

MAY 31, 1991

Date

Thomas Fitting

Thomas Fitting, Reg. No. 34,163

DRESSLER, GOLDSMITH, SHORE
SUTKER & MILNAMOW, LTD.
11300 Sorrento Valley Road
Suite 200
San Diego, California 92121

☒ Attorney or agent of record
☐ Filed Under §1.34(a)

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Zebedee, Suzannne
Inchauspe, Genevieve
Nasoff, Marc
Prince, Alfred
- (ii) TITLE OF INVENTION: NON-A, NON-B HEPATITIS VIRUS ANTIGEN
DIAGNOSTIC METHODS AND VACCINES
- (iii) NUMBER OF SEQUENCES: 45
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: DRESSLER, GOLDSMITH, SHORE, SUTKER &
MILNAMOW, LTD
 - (B) STREET: 11300 Sorrento Valley Road
 - (C) CITY: San Diego
 - (D) STATE: CA
 - (E) COUNTRY: USA
 - (F) ZIP: 92121
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER: US 07/616,369
 - (B) FILING DATE: 21-NOV-1990
 - (C) CLASSIFICATION:
- (v) PRIOR APPLICATION DATA;
 - (A) APPLICATION NUMBER: US 07/573,643
 - (B) FILING DATE: 25-AUG-1990
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Bingham, Douglas A.
 - (B) REGISTRATION NUMBER: 32,457
 - (C) REFERENCE/DOCKET NUMBER: PHA0026P
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: 619-546-1555
 - (B) TELEFAX: 619-546-1380

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 978 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..978
- (D) OTHER INFORMATION: /codon_start= 1
/product= "NANBV Structural Antigen"
/number= 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATG AGC ACG ATT CCC AAA CCT CAA AGA AAA ACC AAA CGT AAC ACC AAC	48
Met Ser Thr Ile Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn	
1 5 10 15	
CGT CGC CCA CAG GAC GTC AAG TTC CCG GGT GGC GGT CAG ATC GTT GGT	96
Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly	
20 25 30	
GGA GTT TAC TTG TTG CCG CGC AGG GGC CCT AGA TTG GGT GTG CGC CGC	144
Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala	
35 40 45	
ACG AGG AAG ACT TCC GAG CGG TCG CAA CCT CGA GGT AGA CGT CAG CCT	192
Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro	
50 55 60	
ATC CCC AAG GCA CGT CGG CCC GAG GGC AGG ACC TGG GCT CAG CCC GGG	240
Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly	
65 70 75 80	
TAC CCT TGG CCC CTC TAT GGC AAT GAG GGT TGC GGG TGG GCG GGA TGG	288
Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp	
85 90 95	
CTC CTG TCT CCC CGT GGC TCT CGG CCT AGC TGG GGC CCC ACA GAC CCC	336
Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro	
100 105 110	

CGG CCT AGG TCG CGC AAT TTG GGT AAG GTC ATC GAT ACC CTT ACG TGC Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys 115 120 125	384
GGC TTC GCC GAC CTC ATG GGG TAC ATA CCG CTC GTC GGC GCC CCT CTT Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu 130 135 140	432
GGA GGC GCT GCC AGG GCC CTG GCG CAT GGC GTC CGG GTT CTG GAA GAC Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp 145 150 155 160	480
GGC GTG AAC TAT GCA ACA GGG AAC CTT CCT GGT TGC TCT TTC TCT ATC Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile 165 170 175	528
TTC CTT CTG GCC CTG CTC TCT TGC CTG ACT GTG CCC GCT TCA GCC TAC Phe Leu Leu Ala Leu Ser Cys Leu Thr Val Pro Ala Ser Ala Tyr 180 185 190	576
CAA GTG CGC AAT TCC TCG GGG CTT TAC CAT GTC ACC AAT GAT TGC CCT Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val Thr Asn Asp Cys Pro 195 200 205	624
AAC TCG AGT GTT GTG TAC GAG GCG GCC GAT GCC ATC CTG CAC ACT CCG Asn Ser Ser Val Val Tyr Glu Ala Ala Asp Ala Ile Leu His Thr Pro 210 215 220	672
GGG TGT GTC CCT TGC GTT CGC GAG GGT AAC GCC TCG AGG TGT TGG GTG Gly Cys Val Pro Cys Val Arg Glu Gly Asn Ala Ser Arg Cys Trp Val 225 230 235 240	720
GGC GTG ACC CCC ACG GTG GCC ACC AGG GAC GGC AAA CTT CCC ACA ACG Ala Val Thr Pro Thr Val Ala Thr Arg Asp Gly Lys Leu Pro Thr Thr 245 250 255	768
CAG CTT CGA CGT CAT ATC GAT CTG CTT GTC GGG AGC GCC ACC CTC TGC Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly Ser Ala Thr Leu Cys 260 265 270	816
TCG GCC CTC TAC GTG GGG GAC CTG TGC GGG TCT GTC TTT CTC GTT GGT Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser Val Phe Leu Val Gly 275 280 285	864
CAA CTG TTT ACC TTC TCT CCC AGG CGC CAC TGG ACG ACG CAA GAC TGC Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp Thr Thr Gln Asp Cys 290 295 300	912
AAT TGT TCT ATC TAT CCC GGC CAT ATA ACG GGT CAT CGC ATG GCA TGG Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His Arg Met Ala Trp 305 310 315 320	960

GAT ATG ATG ATG AAC TGG
 Asp Met Met Met Asn Trp
 325

978

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 948 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..945

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC	48
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro	
1 5 10 15	
ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG	96
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu	
20 25 30	
TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG	144
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu	
35 40 45	
GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA	192
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys	
50 55 60	
TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC	240
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn	
65 70 75 80	
ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA	288
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu	
85 90 95	

GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser 100 105 110	336
AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu 115 120 125	384
ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn 130 135 140	432
GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp 145 150 155 160	480
GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu 165 170 175	528
GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr 180 185 190	576
TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala 195 200 205	624
ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG ATC GAA GGT Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Ile Glu Gly 210 215 220	672
CGT GGG ATC CCC AAT TCG AGC TCG GTA CCC ATG AGC ACG ATT CCC AAA Arg Gly Ile Pro Asn Ser Ser Ser Val Pro Met Ser Thr Ile Pro Lys 225 230 235 240	720
CCT CAA AGA AAA ACC AAA CGT AAC ACC AAC CGT CGC CCA CAG GAC GTC Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp Val 245 250 255	768
AAG TTC CCG GGT GGC GGT CAG ATC GTT GGT GGA GTT TAC TTG TTG CCG Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu Pro 260 265 270	816
CGC AGG GGC CCT AGA TTG GGT GTG CGC GCG ACG AGG AAG ACT TCC GAG Arg Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser Glu 275 280 285	864
CGG TCG CAA CCT CGA GGT AGA CGT CAG CCT ATC CCC AAG GCA CGT CGG Arg Ser Gln Pro Arg Gly Arg Gln Pro Ile Pro Lys Ala Arg Arg 290 295 300	912

CCC GAG GGC AGG ACG GGG ATC GGG AAT TCA TCG TGA
 Pro Glu Gly Arg Thr Gly Ile Gly Asn Ser Ser
 305 310 315

948

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 759 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..756

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC	48
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro	
1 5 10 15	
ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG	96
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu	
20 25 30	
TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG	144
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu	
35 40 45	
GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA	192
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys	
50 55 60	
TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC	240
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn	
65 70 75 80	
ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA	288
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu	
85 90 95	
GGG GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT	336

Gly	Ala	Val	Leu	Asp	Ile	Arg	Tyr	Gly	Val	Ser	Arg	Ile	Ala	Tyr	Ser		
			100					105					110				
AAA	GAC	TTT	GAA	ACT	CTC	AAA	GTT	GAT	TTT	CTT	AGC	AAG	CTA	CCT	GAA	384	
Lys	Asp	Phe	Glu	Thr	Leu	Lys	Val	Asp	Phe	Leu	Ser	Lys	Leu	Pro	Glu		
		115					120					125					
ATG	CTG	AAA	ATG	TTC	GAA	GAT	CGT	TTA	TGT	CAT	AAA	ACA	TAT	TTA	AAT	432	
Met	Leu	Lys	Met	Phe	Glu	Asp	Arg	Leu	Cys	His	Lys	Thr	Tyr	Leu	Asn		
	130						135					140					
GGT	GAT	CAT	GTA	ACC	CAT	CCT	GAC	TTC	ATG	TTG	TAT	GAC	GCT	CTT	GAT	480	
Gly	Asp	His	Val	Thr	His	Pro	Asp	Phe	Met	Leu	Tyr	Asp	Ala	Leu	Asp		
145					150					155				160			
GTT	GTT	TTA	TAC	ATG	GAC	CCA	ATG	TGC	CTG	GAT	CGC	TTC	CCA	AAA	TTA	528	
Val	Val	Leu	Tyr	Met	Asp	Pro	Met	Cys	Leu	Asp	Ala	Phe	Pro	Lys	Leu		
			165					170					175				
GTT	TGT	TTT	AAA	AAA	CGT	ATT	GAA	GCT	ATC	CCA	CAA	ATT	GAT	AAG	TAC	576	
Val	Cys	Phe	Lys	Lys	Arg	Ile	Glu	Ala	Ile	Pro	Gln	Ile	Asp	Lys	Tyr		
		180					185						190				
TTG	AAA	TCC	AGC	AAG	TAT	ATA	GCA	TGG	CCT	TTG	CAG	GGC	TGG	CAA	GCC	624	
Leu	Lys	Ser	Ser	Lys	Tyr	Ile	Ala	Trp	Pro	Leu	Gln	Gly	Trp	Gln	Ala		
	195						200					205					
ACG	TTT	GGT	GGT	GGC	GAC	CAT	CCT	CCA	AAA	TCG	GAT	CTG	GTT	CCG	CGT	672	
Thr	Phe	Gly	Gly	Gly	Asp	His	Pro	Pro	Lys	Ser	Asp	Leu	Val	Pro	Arg		
	210					215					220						
GGA	TCC	ATG	AGC	ACG	ATT	CCC	AAA	CCT	CAA	AGA	AAA	ACC	AAA	CGT	AAC	720	
Gly	Ser	Met	Ser	Thr	Ile	Pro	Lys	Pro	Gln	Arg	Lys	Thr	Lys	Arg	Asn		
225					230				235					240			
ACC	AAC	CGT	CGC	CCA	CAG	GAA	TTC	ATC	GTG	ACT	GAC	TGA				759	
Thr	Asn	Arg	Arg	Pro	Gln	Glu	Phe	Ile	Val	Thr	Asp						
			245					250									

(2) INFORMATION FOR SEQ ID NO:4:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 759 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..756

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ATG TCC CCT ATA CTA GGT TAT TCG AAA ATT AAG GGC CTT GTG CAA CCC	48
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro	
1 5 10 15	
ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG	96
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu	
20 25 30	
TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG	144
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu	
35 40 45	
GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA	192
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys	
50 55 60	
TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC	240
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn	
65 70 75 80	
ATG TTG GGT GGT TGT CCA AAA GAG CGT CCA GAG ATT TCA ATG CTT GAA	288
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu	
85 90 95	
GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT	336
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser	
100 105 110	
AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA	384
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu	
115 120 125	
ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT	432
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn	
130 135 140	
GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT	480
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp	
145 150 155 160	
GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA	528
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu	



98
165 170 175

TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC 576
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190

TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC 624
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205

ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT 672
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220

GGA TCC GAC GTC AAG TTC CCG GGT GGC GGT CAG ATC GTT GGT GGA GTT 720
Gly Ser Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val
225 230 235 240

TAC TTG TTG CCG CGC AGG GAA TTC ATC GTG ACT GAC TGA 759
Tyr Leu Leu Pro Arg Arg Glu Phe Ile Val Thr Asp
245 250

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 759 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..756

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC 48
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15

ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG 96
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
20 25 30

TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu 35 40 45	144
GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys 50 55 60	192
TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn 65 70 75 80	240
ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu 85 90 95	288
GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser 100 105 110	336
AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu 115 120 125	384
ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn 130 135 140	432
GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp 145 150 155 160	480
GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu 165 170 175	528
GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr 180 185 190	576
TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala 195 200 205	624
ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg 210 215 220	672
GGA TCC GGC CCT AGA TTG GGT GTG CGC GCG ACG AGG AAG ACT TCC GAG Gly Ser Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser Glu 225 230 235 240	720

CGG TCG CAA CCT CGA GGT GAA TTC ATC GTG ACT GAC TGA
 Arg Ser Gln Pro Arg Gly Glu Phe Ile Val Thr Asp
 245 250

759

(2) INFORMATION FOR SEQ ID NO:6:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 816 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..813

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC	48
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro	
1 5 10 15	
ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG	96
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu	
20 25 30	
TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG	144
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu	
35 40 45	
GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA	192
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys	
50 55 60	
TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC	240
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn	
65 70 75 80	
ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA	288
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu	
85 90 95	

101

GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser 100 105 110	336
AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu 115 120 125	384
ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn 130 135 140	432
GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp 145 150 155 160	480
GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu 165 170 175	528
GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr 180 185 190	576
TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala 195 200 205	624
ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg 210 215 220	672
GGA TCC AGC ACG ATT CCC AAA CCT CAA AGA AAA ACC AAA CGT AAC ACC Gly Ser Ser Thr Ile Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr 225 230 235 240	720
AAC CGT CGC CCA CAG GAC GTC AAG TTC CCG GGT GGC GGT CAG ATC GTT Asn Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val 245 250 255	768
GGT GGA GTT TAC TTG TTG CCG CGC AGG GAA TTC ATC GTG ACT GAC Gly Gly Val Tyr Leu Leu Pro Arg Arg Glu Phe Ile Val Thr Asp 260 265 270	813
TGA	816

(2) INFORMATION FOR SEQ ID NO:7:

- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 66 base pairs
 - (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GATCCATGAG CACGATTCCC AACCTCAAA GAAAAACCAA ACGTAACACC AACCGTCGCC 60

CACAGG 66

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 66 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

AATTCCTGTG GGCGACGGTT GGTGTTACGT TTGGTTTTTC TTTGAGGTTT GGAATCGTG 60

CTCATG 66

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 66 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GATCGGACGT CAAGTTCCCG GGTGGCGGTC AGATCGTTGG TGGAGTTTAC TTGTTGCCGC 60
GCAGGG 66

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 66 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

AATTCCTGCG GCGGCAAGAA GTAACTCCA CCAACGATCT GACCGCCACC CGGGAACCTG 60
ACGTG 66

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 66 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GATCCGGCCC TAGATTGGGT GTGCCGCCGA CGAGGAAGAC TTCCGAGCGG TCGCAACCTC 60
GAGGTG 66

(2) INFORMATION FOR SEQ ID NO:12:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 66 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AATTCACCTC GAGGTTGCGA CCGCTCGGAA GTCTTCCTCG TCGCGCGCAC ACCCAATCTA 60
GGGCGG 66

(2) INFORMATION FOR SEQ ID NO:13:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCTTAC CTGCGCGGCA ACAAGTAAAC TC 32

(2) INFORMATION FOR SEQ ID NO:14:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GCTGGATCCA GCACGATTCC CAAACCTCAA AG

32

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATGAGCACGA TTCCCAAACC T

21

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GAGGAAGACT TCCGAGC

17

(2) INFORMATION FOR SEQ ID NO:17:

- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GTCTGCCCCT CGGGCCG

17

(2) INFORMATION FOR SEQ ID NO:18:

- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

ACCCAAATTG CGCGACCTAC G

21

(2) INFORMATION FOR SEQ ID NO:19:

- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TGGGTAAGGT CATCGATAC

19

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AAGGTCATCG ATACCCCT

17

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

AGATAGAGAA AGAGCAAC

19

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GGACCACTTC ATCATCATAT AT

22

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CAGTTCATCA TCATATCCCA

20

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..15

(D) OTHER INFORMATION: /product= "Linker Protein in
GST-NANBV 693-691"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

G G G A T C C C C A A T T C A
G l y I l e P r o A s n S e r
1 5

15

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

G l y I l e P r o A s n S e r
1 5

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..9
(D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
Protein in GST-NANBV 693-691"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

A A T T C A T C G T G A
A s n S e r S e r

12

1

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 3 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Asn Ser Ser

1

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..27
- (D) OTHER INFORMATION: /product= "Linker Protein in GST-NANBV 15-18"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGG ATC CCC ATC GAA TTC CTG CAG CCC
 Gly Ile Pro Ile Glu Phe Leu Gln Pro
 1 5

2

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 9 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

111

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Gly Ile Pro Ile Glu Phe Leu Gln Pro
1 5

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..21
(D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
Protein in GST-NANBV 15-18"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

TGG GGG ATC GGG AAT TCA TCG TGA
Trp Gly Ile Gly Asn Ser Ser
1 5

24

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Trp Gly Ile Gly Asn Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:32:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..24
- (D) OTHER INFORMATION: /product= "Linker Protein in GST-NANBV 15-17"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GGG ATC CCC AAT TCC TGC AGC CCT
 Gly Ile Pro Asn Ser Cys Ser Pro
 1 5

24

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Gly Ile Pro Asn Ser Cys Ser Pro
 1 5

(2) INFORMATION FOR SEQ ID NO:34:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..18

(D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
Protein in GST-NANBV 15-17"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

G G G A T C G G G A A T T C A T C G T G A

G l y I l e G l y A s n S e r S e r

1

5

21

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

G l y I l e G l y A s n S e r S e r

1

5

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..15

(D) OTHER INFORMATION: /product= "Thrombin Cleavage Site"

in GST-NANBV 15-17"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTT CCG CGT GGA TCC
Val Pro Arg Gly Ser
1 5

15

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Val Pro Arg Gly Ser
1 5

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..21
(D) OTHER INFORMATION: /product= "Linker Protein in
GST-NANBV 15-17"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CCA TCG AAT TCC TGC AGC CCT
Pro Ser Asn Ser Cys Ser Pro
1 5

21

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 7 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Pro Ser Asn Ser Cys Ser Pro
 1 5

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..15
- (D) OTHER INFORMATION: /product= "Carboxy-terminal Linker Protein in GST-NANBV 15-17"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GGA ATT CAT CGT GAC TGA
 Gly Ile His Arg Asp
 1 5

18

(2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 5 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Gly Ile His Arg Asp
 1 5

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..27
- (D) OTHER INFORMATION: /product= "Linker Protein in GST-NANBV 690-691"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GGG ATC CCC AAT TCG AGC TCG GTA CCC
 Gly Ile Pro Asn Ser Ser Ser Val Pro
 1 5

2

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Gly Ile Pro Asn Ser Ser Ser Val Pro
 1 5

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

117

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..21
- (D) OTHER INFORMATION: /product= "Carboxy-terminal Linker Protein in GST-NANBV 690-691"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

ACG GGG ATC GGG AAT TCA TCG TGA
Thr Gly Ile Gly Asn Ser Ser
1 5

24

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Thr Gly Ile Gly Asn Ser Ser
1 5

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JUN 10 1991

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date indicated below with sufficient postage as First Class Mail in an envelope addressed to: Honorable Commissioner of Patents and Trademarks, Box Sequence, Washington, D.C. 20231, Attn: Dora Stroud, Application Processing Division.

Thomas Fitting
Thomas Fitting, Reg. No. 34,163

May 31, 1991
Date of Deposit

Applicant: Zebedee et al.

Serial No.: 07/616,369

Filed: November 21, 1990

For: NON-A, NON-B HEPATITIS VIRUS
ANTIGENS, DIAGNOSTIC METHODS
AND VACCINES

Group Art Unit:
Unassigned

Examiner: Unassigned

Our Ref. No. PHA 0026P
San Diego, California

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Transmitted herewith is/are the following document(s) related to
the above-identified patent application:

- | | |
|--|----------------------------------|
| (X) Acknowledgement of Receipt Card | () Request for Reconsideration |
| () Disclosure Statement/37 CFR 1.56 | () Affidavit Under 37 CFR 1.131 |
| (X) Preliminary Amendment | () Affidavit Under 37 CFR 1.132 |
| (X) <u>4</u> Month Extension of Time Under | () Notice of Appeal |
| 37 CFR 1.136 (fee noted on | () Appeal Brief (in triplicate) |
| Petition attached) | () Reply Brief |
| () Response Under 37 CFR 1.111 | (X) Certificate of Mailing |
| () Amendment Under 37 CFR 1.115 | () Communication |
| () Amendment After Final Rejection | () Change of Address in |
| Under 37 CFR 1.116 | Application |
| () Power of Attorney by Inventor | () Assignment |
| (X) Other: Response to Notice to Comply | (X) Computer Readable Floppy |
| with Requirements for Patent | Diskette Containing |
| applications Containing Nucleotide | Sequence Listing and paper |
| Sequence and/or Amino Acid Sequence | copy of the Sequence Listing |
| Disclosures (37 CFR 1.821-1.825) | |

() No additional fee is required.

090 KP 06/07/91 07616349

1 118 1-150.00 CR


Serial No. 07/616,369

-2-

The Commissioner is hereby authorized to charge payment of any additional patent application filing fees under 37 CFR §1.16, 37 CFR §1.17, or patent issue fee under 37 CFR §1.18 associated with this communication or credit any overpayment to Deposit Account No. 04-1644.

May 31, 1991

(Date)


Thomas Fitting, Reg. No. 34,163

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A:\C:\QA\PHA26SEQ.TRL/AF

Patent Application US/07/616,369

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Zebedee, Suzanne
Inchauspe, Genevieve
Nasoff, Marc
Prince, Alfred

(ii) TITLE OF INVENTION: NON-A, NON-B HEPATITIS VIRUS ANTIGEN,
DIAGNOSTIC METHODS AND VACCINES

(iii) NUMBER OF SEQUENCES: 45

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: DRESSLER, GOLDSMITH, SHORE, SUTKER &
MILNAMOW, LTD
(B) STREET: 11300 Sorrento Valley Road
(C) CITY: San Diego
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 92121

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/616,369
(B) FILING DATE: 21-NOV-1990
(C) CLASSIFICATION:

(v) PRIOR APPLICATION DATA: *fixed by systems branch*

(A) APPLICATION NUMBER: US 07/573,643
(B) FILING DATE: 25-AUG-1990
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Bingham, Douglas A.
(B) REGISTRATION NUMBER: 32,457
(C) REFERENCE/DOCKET NUMBER: PHA0026P

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 619-546-1555
(B) TELEFAX: 619-546-1380

(2) INFORMATION FOR SEQ ID NO:1:

Patent Application US/07/616,369

54 (i) SEQUENCE CHARACTERISTICS:
55 (A) LENGTH: 978 base pairs
56 (B) TYPE: nucleic acid
57 (C) STRANDEDNESS: single
58 (D) TOPOLOGY: linear
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60 (ii) MOLECULE TYPE: DNA (genomic)
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62 (iii) HYPOTHETICAL: NO
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64 (iv) ANTI-SENSE: NO
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67 (ix) FEATURE:
68 (A) NAME/KEY: CDS
69 (B) LOCATION: 1..978
70 (D) OTHER INFORMATION: /codon_start= 1
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87 Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
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Raw Sequence Listing

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ge: 4

Raw Sequence Listing
Patent Application US/07/616,369

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163 (2) INFORMATION FOR SEQ ID NO:2:
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166 (A) LENGTH: 948 base pairs
167 (B) TYPE: nucleic acid
168 (C) STRANDEDNESS: single
169 (D) TOPOLOGY: linear
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171 (ii) MOLECULE TYPE: DNA (genomic)
172
173 (iii) HYPOTHETICAL: NO
174
175 (iv) ANTI-SENSE: NO
176
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178 (ix) FEATURE:
179 (A) NAME/KEY: CDS
180 (B) LOCATION: 1..945
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183 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
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266 (2) INFORMATION FOR SEQ ID NO:3:
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268 (i) SEQUENCE CHARACTERISTICS:
269 (A) LENGTH: 759 base pairs
270 (B) TYPE: nucleic acid
271 (C) STRANDEDNESS: single
272 (D) TOPOLOGY: linear
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274 (ii) MOLECULE TYPE: DNA (genomic)
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276 (iii) HYPOTHETICAL: NO
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278 (iv) ANTI-SENSE: NO
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281 (ix) FEATURE:
282 (A) NAME/KEY: CDS
283 (B) LOCATION: 1..756
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Page: 7

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06/13/91
14:56:15

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(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
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 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: NO
- (iv) ANTI-SENSE: NO
- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 1..756

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06/13/91
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440 (2) INFORMATION FOR SEQ ID NO:5:
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442 (i) SEQUENCE CHARACTERISTICS:
443 (A) LENGTH: 759 base pairs
444 (B) TYPE: nucleic acid
445 (C) STRANDEDNESS: single
446 (D) TOPOLOGY: linear
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448 (ii) MOLECULE TYPE: DNA (genomic)
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450 (iii) HYPOTHETICAL: NO
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452 (iv) ANTI-SENSE: NO
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455 (ix) FEATURE:
456 (A) NAME/KEY: CDS
457 (B) LOCATION: 1..756
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460 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:
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471 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu    144
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06/13/91

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505		
506	GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC	
507	Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr	576
508	180 185 190	
509		
510	TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC	
511	Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala	624
512	195 200 205	
513		
514	ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT	
515	Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg	672
516	210 215 220	
517		
518	GGA TCC GGC CCT AGA TTG GGT GTG CGC GCG ACG AGG AAG ACT TCC GAG	
519	Gly Ser Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser Glu	720
520	225 230 235 240	
521		
522	CGG TCG CAA CCT CGA GGT GAA TTC ATC GTG ACT GAC TGA	
523	Arg Ser Gln Pro Arg Gly Glu Phe Ile Val Thr Asp	759
524	245 250	
525		
526		
527	(2) INFORMATION FOR SEQ ID NO:6:	
528		
529	(i) SEQUENCE CHARACTERISTICS:	
530	(A) LENGTH: 816 base pairs	

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531 (B) TYPE: nucleic acid
532 (C) STRANDEDNESS: single
533 (D) TOPOLOGY: linear
534
535 (ii) MOLECULE TYPE: DNA (genomic)
536
537 (iii) HYPOTHETICAL: NO
538
539 (iv) ANTI-SENSE: NO
540
541
542 (ix) FEATURE:
543 (A) NAME/KEY: CDS
544 (B) LOCATION: 1..813
545
546
547 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:
548
549 ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC 48
550 Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
551 1 5 10 15
552
553 ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG 96
554 Thr Arg Leu Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
555 20 25 30
556
557 TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG 144
558 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
559 35 40 45
560
561 GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA 192
562 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
563 50 55 60
564
565 TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC 240
566 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
567 65 70 75 80
568
569 ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA 288
570 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
571 85 90 95
572
573 GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT 336
574 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
575 100 105 110
576
577 AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA 384
578 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
579 115 120 125
580
581 ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT 432
582 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
583 130 135 140

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584
585 GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT 480
586 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
587 145 150 155 160
588
589 GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA 528
590 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
591 165 170 175
592
593 GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC 576
594 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
595 180 185 190
596
597 TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC 624
598 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
599 195 200 205
600
601 ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT 672
602 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
603 210 215 220
604
605 GGA TCC AGC ACG ATT CCC AAA CCT CAA AGA AAA ACC AAA CGT AAC ACC 720
606 Gly Ser Ser Thr Ile Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr
607 225 230 235 240
608
609 AAC CGT CGC CCA CAG GAC GTC AAG TTC CCG GGT GGC GGT CAG ATC GTT 768
610 Asn Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val
611 245 250 255
612
613 GGT GGA GTT TAC TTG TTG CCG CGC AGG GAA TTC ATC GTG ACT GAC 813
614 Gly Gly Val Tyr Leu Leu Pro Arg Arg Glu Phe Ile Val Thr Asp
615 260 265 270
616
617 TGA 816
618
619

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 66 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

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637
638 GATCCATGAG CACGATTCCTC AAACCTCAAA GAAAAACCAA ACGTAACACC AACCGTCGCC 60
639
640 CACAGG 66
641
642 (2) INFORMATION FOR SEQ ID NO:8:
643
644 (i) SEQUENCE CHARACTERISTICS:
645 (A) LENGTH: 66 base pairs
646 (B) TYPE: nucleic acid
647 (C) STRANDEDNESS: single
648 (D) TOPOLOGY: linear
649
650 (ii) MOLECULE TYPE: DNA (genomic)
651
652 (iii) HYPOTHETICAL: NO
653
654 (iv) ANTI-SENSE: NO
655
656
657
658 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:
659
660 AATTCCTGTG GCGGACGGTT GGTGTTACGT TTGTTTTTC TTGAGGTTT GCGAATCGTG 60
661
662 CTCATG 66
663
664 (2) INFORMATION FOR SEQ ID NO:9:
665
666 (i) SEQUENCE CHARACTERISTICS:
667 (A) LENGTH: 66 base pairs
668 (B) TYPE: nucleic acid
669 (C) STRANDEDNESS: single
670 (D) TOPOLOGY: linear
671
672 (ii) MOLECULE TYPE: DNA (genomic)
673
674 (iii) HYPOTHETICAL: NO
675
676 (iv) ANTI-SENSE: NO
677
678
679
680 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
681
682 GATCCGACGT CAAGTTCCCG GGTGGCGGTC AGATCGTTGG TGGAGTTTAC TTGTTGCCGC 60
683
684 GCAGGG 66
685
686 (2) INFORMATION FOR SEQ ID NO:10:
687
688 (i) SEQUENCE CHARACTERISTICS:
689 (A) LENGTH: 66 base pairs

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690 (B) TYPE: nucleic acid
691 (C) STRANDEDNESS: single
692 (D) TOPOLOGY: linear
693
694 (ii) MOLECULE TYPE: DNA (genomic)
695
696 (iii) HYPOTHETICAL: NO
697
698 (iv) ANTI-SENSE: NO
699
700
701
702 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
703
704 AATTCCTGCG GCGGCAACAA GTAACTCCA CCAACGATCT GACCGCCACC CGGGAACTTG 60
705
706 ACGTCG 66
707
708 (2) INFORMATION FOR SEQ ID NO:11:
709
710 (i) SEQUENCE CHARACTERISTICS:
711 (A) LENGTH: 66 base pairs
712 (B) TYPE: nucleic acid
713 (C) STRANDEDNESS: single
714 (D) TOPOLOGY: linear
715
716 (ii) MOLECULE TYPE: DNA (genomic)
717
718 (iii) HYPOTHETICAL: NO
719
720 (iv) ANTI-SENSE: NO
721
722
723
724 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:
725
726 GATCCGGCCC TAGATTGGGT GTGCGCGCGA CGAGGAAGAC TTCCGAGCGG TCGCAACCTC 60
727
728 GAGGTC 66
729
730 (2) INFORMATION FOR SEQ ID NO:12:
731
732 (i) SEQUENCE CHARACTERISTICS:
733 (A) LENGTH: 66 base pairs
734 (B) TYPE: nucleic acid
735 (C) STRANDEDNESS: single
736 (D) TOPOLOGY: linear
737
738 (ii) MOLECULE TYPE: DNA (genomic)
739
740 (iii) HYPOTHETICAL: NO
741
742 (iv) ANTI-SENSE: NO

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743
744
745
746 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:
747
748 AATTCACCTC GAGGTGCGA CCGCTCGGAA GTCTTCCTCG TCGCGCGCAC ACCCAATCTA 60
749
750 GGGCCG 66
751
752 (2) INFORMATION FOR SEQ ID NO:13:
753
754 (i) SEQUENCE CHARACTERISTICS:
755 (A) LENGTH: 32 base pairs
756 (B) TYPE: nucleic acid
757 (C) STRANDEDNESS: single
758 (D) TOPOLOGY: linear
759
760 (ii) MOLECULE TYPE: DNA (genomic)
761
762 (iii) HYPOTHETICAL: NO
763
764 (iv) ANTI-SENSE: NO
765
766
767
768 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:
769
770 GAATTCCTAC CTGCGCGGCA ACAAGTAAAC TC 32
771
772 (2) INFORMATION FOR SEQ ID NO:14:
773
774 (i) SEQUENCE CHARACTERISTICS:
775 (A) LENGTH: 32 base pairs
776 (B) TYPE: nucleic acid
777 (C) STRANDEDNESS: single
778 (D) TOPOLOGY: linear
779
780 (ii) MOLECULE TYPE: DNA (genomic)
781
782 (iii) HYPOTHETICAL: NO
783
784 (iv) ANTI-SENSE: NO
785
786
787
788 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:
789
790 GCTGGATCCA GCACGATTCC CAAACCTCAA AG 32
791
792 (2) INFORMATION FOR SEQ ID NO:15:
793
794 (i) SEQUENCE CHARACTERISTICS:
795 (A) LENGTH: 21 base pairs

796 (B) TYPE: nucleic acid
797 (C) STRANDEDNESS: single
798 (D) TOPOLOGY: linear
799
800 (ii) MOLECULE TYPE: DNA (genomic)
801
802 (iii) HYPOTHETICAL: NO
803
804 (iv) ANTI-SENSE: NO
805
806
807
808 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:
809
810 ATGAGCACGA TTCCCAAACC T
811
812 (2) INFORMATION FOR SEQ ID NO:16:
813
814 (i) SEQUENCE CHARACTERISTICS:
815 (A) LENGTH: 17 base pairs
816 (B) TYPE: nucleic acid
817 (C) STRANDEDNESS: single
818 (D) TOPOLOGY: linear
819
820 (ii) MOLECULE TYPE: DNA (genomic)
821
822 (iii) HYPOTHETICAL: NO
823
824 (iv) ANTI-SENSE: NO
825
826
827
828 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:
829
830 GAGGAAGACT TCCGAGC
831
832 (2) INFORMATION FOR SEQ ID NO:17:
833
834 (i) SEQUENCE CHARACTERISTICS:
835 (A) LENGTH: 17 base pairs
836 (B) TYPE: nucleic acid
837 (C) STRANDEDNESS: single
838 (D) TOPOLOGY: linear
839
840 (ii) MOLECULE TYPE: DNA (genomic)
841
842 (iii) HYPOTHETICAL: NO
843
844 (iv) ANTI-SENSE: YES
845
846
847
848 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

21

17

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849
850 GTCCTGCCCT CGGGCCG 17
851
852 (2) INFORMATION FOR SEQ ID NO:18:
853
854 (i) SEQUENCE CHARACTERISTICS:
855 (A) LENGTH: 21 base pairs
856 (B) TYPE: nucleic acid
857 (C) STRANDEDNESS: single
858 (D) TOPOLOGY: linear
859
860 (ii) MOLECULE TYPE: DNA (genomic)
861
862 (iii) HYPOTHETICAL: NO
863
864 (iv) ANTI-SENSE: YES
865
866
867
868 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:
869
870 ACCCAAATTG CGCGACCTAC G 21
871
872 (2) INFORMATION FOR SEQ ID NO:19:
873
874 (i) SEQUENCE CHARACTERISTICS:
875 (A) LENGTH: 19 base pairs
876 (B) TYPE: nucleic acid
877 (C) STRANDEDNESS: single
878 (D) TOPOLOGY: linear
879
880 (ii) MOLECULE TYPE: DNA (genomic)
881
882 (iii) HYPOTHETICAL: NO
883
884 (iv) ANTI-SENSE: NO
885
886
887
888 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:
889
890 TGGGTAAGGT CATCGATAC 19
891
892 (2) INFORMATION FOR SEQ ID NO:20:
893
894 (i) SEQUENCE CHARACTERISTICS:
895 (A) LENGTH: 17 base pairs
896 (B) TYPE: nucleic acid
897 (C) STRANDEDNESS: single
898 (D) TOPOLOGY: linear
899
900 (ii) MOLECULE TYPE: DNA (genomic)
901

902 (iii) HYPOTHETICAL: NO
903
904 (iv) ANTI-SENSE: NO
905
906
907
908 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:
909
910 AAGGTCATCG ATACCCCT 17
911
912 (2) INFORMATION FOR SEQ ID NO:21:
913
914 (i) SEQUENCE CHARACTERISTICS:
915 (A) LENGTH: 18 base pairs
916 (B) TYPE: nucleic acid
917 (C) STRANDEDNESS: single
918 (D) TOPOLOGY: linear
919
920 (ii) MOLECULE TYPE: DNA (genomic)
921
922 (iii) HYPOTHETICAL: NO
923
924 (iv) ANTI-SENSE: YES
925
926
927
928 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:
929
930 AGATAGAGAA AGAGCAAC 19
931
932 (2) INFORMATION FOR SEQ ID NO:22:
933
934 (i) SEQUENCE CHARACTERISTICS:
935 (A) LENGTH: 22 base pairs
936 (B) TYPE: nucleic acid
937 (C) STRANDEDNESS: single
938 (D) TOPOLOGY: linear
939
940 (ii) MOLECULE TYPE: DNA (genomic)
941
942 (iii) HYPOTHETICAL: NO
943
944 (iv) ANTI-SENSE: YES
945
946
947
948 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:
949
950 GGACCAGTTC ATCATCATAT AT 22
951
952 (2) INFORMATION FOR SEQ ID NO:23:
953
954 (i) SEQUENCE CHARACTERISTICS:

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955 (A) LENGTH: 20 base pairs
956 (B) TYPE: nucleic acid
957 (C) STRANDEDNESS: single
958 (D) TOPOLOGY: linear
959
960 (ii) MOLECULE TYPE: DNA (genomic)
961
962 (iii) HYPOTHETICAL: NO
963
964 (iv) ANTI-SENSE: YES
965
966
967
968 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:
969
970 CAGTTCATCA TCATATCCCA 20
971
972 (2) INFORMATION FOR SEQ ID NO:24:
973
974 (i) SEQUENCE CHARACTERISTICS:
975 (A) LENGTH: 15 base pairs
976 (B) TYPE: nucleic acid
977 (C) STRANDEDNESS: single
978 (D) TOPOLOGY: linear
979
980 (ii) MOLECULE TYPE: DNA (genomic)
981
982 (iii) HYPOTHETICAL: NO
983
984 (iv) ANTI-SENSE: NO
985
986
987 (ix) FEATURE:
988 (A) NAME/KEY: CDS
989 (B) LOCATION: 1..15
990 (D) OTHER INFORMATION: /product= "Linker Protein in
991 GST-NANBV 693-691"
992
993
994 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:
995
996 GGG ATC CCC AAT TCA 15
997 Gly Ile Pro Asn Ser
998 1 5
999
1000
1001 (2) INFORMATION FOR SEQ ID NO:25:
1002
1003 (i) SEQUENCE CHARACTERISTICS:
1004 (A) LENGTH: 5 amino acids
1005 (B) TYPE: amino acid
1006 (D) TOPOLOGY: linear
1007

1008 (ii) MOLECULE TYPE: protein
1009
1010 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:
1011
1012 Gly Ile Pro Asn Ser
1013 1 5
1014
1015 (2) INFORMATION FOR SEQ ID NO:26:
1016
1017 (i) SEQUENCE CHARACTERISTICS:
1018 (A) LENGTH: 12 base pairs
1019 (B) TYPE: nucleic acid
1020 (C) STRANDEDNESS: single
1021 (D) TOPOLOGY: linear
1022
1023 (ii) MOLECULE TYPE: DNA (genomic)
1024
1025 (iii) HYPOTHETICAL: NO
1026
1027 (iv) ANTI-SENSE: NO
1028
1029
1030 (ix) FEATURE:
1031 (A) NAME/KEY: CDS
1032 (B) LOCATION: 1..9
1033 (D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
1034 Protein in GST-NANBV 693-691"
1035
1036
1037 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:
1038
1039 AAT TCA TCG TGA
1040 Asn Ser Ser
1041 1
1042
1043
1044 (2) INFORMATION FOR SEQ ID NO:27:
1045
1046 (i) SEQUENCE CHARACTERISTICS:
1047 (A) LENGTH: 3 amino acids
1048 (B) TYPE: amino acid
1049 (D) TOPOLOGY: linear
1050
1051 (ii) MOLECULE TYPE: protein
1052
1053 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:
1054
1055 Asn Ser Ser
1056 1
1057
1058 (2) INFORMATION FOR SEQ ID NO:28:
1059
1060 (i) SEQUENCE CHARACTERISTICS:

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1061 (A) LENGTH: 27 base pairs
1062 (B) TYPE: nucleic acid
1063 (C) STRANDEDNESS: single
1064 (D) TOPOLOGY: linear
1065
1066 (ii) MOLECULE TYPE: DNA (genomic)
1067
1068 (iii) HYPOTHETICAL: NO
1069
1070 (iv) ANTI-SENSE: NO
1071
1072
1073 (ix) FEATURE:
1074 (A) NAME/KEY: CDS
1075 (B) LOCATION: 1..27
1076 (D) OTHER INFORMATION: /product= "Linker Protein in
1077 GST-NANBV 15-18"
1078
1079
1080 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:
1081
1082 GGG ATC CCC ATC GAA TTC CTG CAG CCC
1083 Gly Ile Pro Ile Glu Phe Leu Gln Pro
1084 1 5
1085
1086
1087 (2) INFORMATION FOR SEQ ID NO:29:
1088
1089 (i) SEQUENCE CHARACTERISTICS:
1090 (A) LENGTH: 9 amino acids
1091 (B) TYPE: amino acid
1092 (D) TOPOLOGY: linear
1093
1094 (ii) MOLECULE TYPE: protein
1095
1096 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:
1097
1098 Gly Ile Pro Ile Glu Phe Leu Gln Pro
1099 1 5
1100
1101 (2) INFORMATION FOR SEQ ID NO:30:
1102
1103 (i) SEQUENCE CHARACTERISTICS:
1104 (A) LENGTH: 24 base pairs
1105 (B) TYPE: nucleic acid
1106 (C) STRANDEDNESS: single
1107 (D) TOPOLOGY: linear
1108
1109 (ii) MOLECULE TYPE: DNA (genomic)
1110
1111 (iii) HYPOTHETICAL: NO
1112
1113 (iv) ANTI-SENSE: NO

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1114
1115
1116 (ix) FEATURE:
1117 (A) NAME/KEY: CDS
1118 (B) LOCATION: 1..21
1119 (D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
1120 Protein in GST-NANBV 15-18"
1121
1122
1123 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:
1124
1125 TGG GGG ATC GGG AAT TCA TCG TGA 24
1126 Trp Gly Ile Gly Asn Ser Ser
1127 1 5
1128
1129
1130 (2) INFORMATION FOR SEQ ID NO:31:
1131
1132 (i) SEQUENCE CHARACTERISTICS:
1133 (A) LENGTH: 7 amino acids
1134 (B) TYPE: amino acid
1135 (D) TOPOLOGY: linear
1136
1137 (ii) MOLECULE TYPE: protein
1138
1139 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:
1140
1141 Trp Gly Ile Gly Asn Ser Ser
1142 1 5
1143
1144 (2) INFORMATION FOR SEQ ID NO:32:
1145
1146 (i) SEQUENCE CHARACTERISTICS:
1147 (A) LENGTH: 24 base pairs
1148 (B) TYPE: nucleic acid
1149 (C) STRANDEDNESS: single
1150 (D) TOPOLOGY: linear
1151
1152 (ii) MOLECULE TYPE: DNA (genomic)
1153
1154 (iii) HYPOTHETICAL: NO
1155
1156 (iv) ANTI-SENSE: NO
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1158
1159 (ix) FEATURE:
1160 (A) NAME/KEY: CDS
1161 (B) LOCATION: 1..24
1162 (D) OTHER INFORMATION: /product= "Linker Protein in
1163 GST-NANBV 15-17"
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1165
1166 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

1167
1168 GGG ATC CCC AAT TCC TGC AGC CCT 24
1169 Gly Ile Pro Asn Ser Cys Ser Pro
1170 1 5
1171
1172
1173 (2) INFORMATION FOR SEQ ID NO:33:
1174
1175 (i) SEQUENCE CHARACTERISTICS:
1176 (A) LENGTH: 8 amino acids
1177 (B) TYPE: amino acid
1178 (D) TOPOLOGY: linear
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1180 (ii) MOLECULE TYPE: protein
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1182 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
1183
1184 Gly Ile Pro Asn Ser Cys Ser Pro
1185 1 5
1186
1187 (2) INFORMATION FOR SEQ ID NO:34:
1188
1189 (i) SEQUENCE CHARACTERISTICS:
1190 (A) LENGTH: 21 base pairs
1191 (B) TYPE: nucleic acid
1192 (C) STRANDEDNESS: single
1193 (D) TOPOLOGY: linear
1194
1195 (ii) MOLECULE TYPE: DNA (genomic)
1196
1197 (iii) HYPOTHETICAL: NO
1198
1199 (iv) ANTI-SENSE: NO
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1202 (ix) FEATURE:
1203 (A) NAME/KEY: CDS
1204 (B) LOCATION: 1..18
1205 (D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
1206 Protein in GST-NANBV 15-17"
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1208
1209 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:
1210
1211 GGG ATC GGG AAT TCA TCG TGA 21
1212 Gly Ile Gly Asn Ser Ser
1213 1 5
1214
1215
1216 (2) INFORMATION FOR SEQ ID NO:35:
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1218 (i) SEQUENCE CHARACTERISTICS:
1219 (A) LENGTH: 6 amino acids

1220 (B) TYPE: amino acid
1221 (D) TOPOLOGY: linear
1222
1223 (ii) MOLECULE TYPE: protein
1224
1225 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:
1226
1227 Gly Ile Gly Asn Ser Ser
1228 1 5
1229
1230 (2) INFORMATION FOR SEQ ID NO:36:
1231
1232 (i) SEQUENCE CHARACTERISTICS:
1233 (A) LENGTH: 15 base pairs
1234 (B) TYPE: nucleic acid
1235 (C) STRANDEDNESS: single
1236 (D) TOPOLOGY: linear
1237
1238 (ii) MOLECULE TYPE: DNA (genomic)
1239
1240 (iii) HYPOTHETICAL: NO
1241
1242 (iv) ANTI-SENSE: NO
1243
1244
1245 (ix) FEATURE:
1246 (A) NAME/KEY: CDS
1247 (B) LOCATION: 1..15
1248 (D) OTHER INFORMATION: /product= "Thrombin Cleavage Site
1249 in GST-NANBV 15-17"
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1251
1252 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:
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1254 GTT CCG CGT GGA TCC
1255 Val Pro Arg Gly Ser
1256 1 5
1257
1258
1259 (2) INFORMATION FOR SEQ ID NO:37:
1260
1261 (i) SEQUENCE CHARACTERISTICS:
1262 (A) LENGTH: 5 amino acids
1263 (B) TYPE: amino acid
1264 (D) TOPOLOGY: linear
1265
1266 (ii) MOLECULE TYPE: protein
1267
1268 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:
1269
1270 Val Pro Arg Gly Ser
1271 1 5
1272

Raw Sequence Listing
Patent Application US/07/616,36906/13/91
14:58:29

1273 (2) INFORMATION FOR SEQ ID NO:38:
1274
1275 (i) SEQUENCE CHARACTERISTICS:
1276 (A) LENGTH: 21 base pairs
1277 (B) TYPE: nucleic acid
1278 (C) STRANDEDNESS: single
1279 (D) TOPOLOGY: linear
1280
1281 (ii) MOLECULE TYPE: DNA (genomic)
1282
1283 (iii) HYPOTHETICAL: NO
1284
1285 (iv) ANTI-SENSE: NO
1286
1287
1288 (ix) FEATURE:
1289 (A) NAME/KEY: CDS
1290 (B) LOCATION: 1..21
1291 (D) OTHER INFORMATION: /product= "Linker Protein in
1292 GST-NANBV 15-17"
1293
1294
1295 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:
1296
1297 CCA TCG AAT TCC TGC AGC CCT
1298 Pro Ser Asn Ser Cys Ser Pro
1299 1 5
1300
1301
1302 (2) INFORMATION FOR SEQ ID NO:39:
1303
1304 (i) SEQUENCE CHARACTERISTICS:
1305 (A) LENGTH: 7 amino acids
1306 (B) TYPE: amino acid
1307 (D) TOPOLOGY: linear
1308
1309 (ii) MOLECULE TYPE: protein
1310
1311 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:
1312
1313 Pro Ser Asn Ser Cys Ser Pro
1314 1 5
1315
1316 (2) INFORMATION FOR SEQ ID NO:40:
1317
1318 (i) SEQUENCE CHARACTERISTICS:
1319 (A) LENGTH: 18 base pairs
1320 (B) TYPE: nucleic acid
1321 (C) STRANDEDNESS: single
1322 (D) TOPOLOGY: linear
1323
1324 (ii) MOLECULE TYPE: DNA (genomic)
1325

1326 (iii) HYPOTHETICAL: NO
1327
1328 (iv) ANTI-SENSE: NO
1329
1330
1331 (ix) FEATURE:
1332 (A) NAME/KEY: CDS
1333 (B) LOCATION: 1..15
1334 (D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
1335 Protein in GST-NANBV 15-17"
1336
1337
1338 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:
1339
1340 GGA ATT CAT CGT GAC TGA
1341 Gly Ile His Arg Asp
1342 1 5
1343
1344
1345 (2) INFORMATION FOR SEQ ID NO:41:
1346
1347 (i) SEQUENCE CHARACTERISTICS:
1348 (A) LENGTH: 5 amino acids
1349 (B) TYPE: amino acid
1350 (D) TOPOLOGY: linear
1351
1352 (ii) MOLECULE TYPE: protein
1353
1354 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:
1355
1356 Gly Ile His Arg Asp
1357 1 5
1358
1359 (2) INFORMATION FOR SEQ ID NO:42:
1360
1361 (i) SEQUENCE CHARACTERISTICS:
1362 (A) LENGTH: 27 base pairs
1363 (B) TYPE: nucleic acid
1364 (C) STRANDEDNESS: single
1365 (D) TOPOLOGY: linear
1366
1367 (ii) MOLECULE TYPE: DNA (genomic)
1368
1369 (iii) HYPOTHETICAL: NO
1370
1371 (iv) ANTI-SENSE: NO
1372
1373
1374 (ix) FEATURE:
1375 (A) NAME/KEY: CDS
1376 (B) LOCATION: 1..27
1377 (D) OTHER INFORMATION: /product= "Linker Protein in
1378 GST-NANBV 690-691"

Raw Sequence Listing
Patent Application US/07/616,36906/13/91
14:58:43

1379
1380
1381 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:
1382
1383 GGG ATC CCC AAT TCG AGC TCG GTA CCC 27
1384 Gly Ile Pro Asn Ser Ser Ser Val Pro
1385 1 5
1386
1387
1388 (2) INFORMATION FOR SEQ ID NO:43:
1389
1390 (i) SEQUENCE CHARACTERISTICS:
1391 (A) LENGTH: 9 amino acids
1392 (B) TYPE: amino acid
1393 (D) TOPOLOGY: linear
1394
1395 (ii) MOLECULE TYPE: protein
1396
1397 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:
1398
1399 Gly Ile Pro Asn Ser Ser Ser Val Pro
1400 1 5
1401
1402 (2) INFORMATION FOR SEQ ID NO:44:
1403
1404 (i) SEQUENCE CHARACTERISTICS:
1405 (A) LENGTH: 24 base pairs
1406 (B) TYPE: nucleic acid
1407 (C) STRANDEDNESS: single
1408 (D) TOPOLOGY: linear
1409
1410 (ii) MOLECULE TYPE: DNA (genomic)
1411
1412 (iii) HYPOTHETICAL: NO
1413
1414 (iv) ANTI-SENSE: NO
1415
1416
1417 (ix) FEATURE:
1418 (A) NAME/KEY: CDS
1419 (B) LOCATION: 1..21
1420 (D) OTHER INFORMATION: /product= "Carboxy-terminal Linker
1421 Protein in GST-NANBV 690-691"
1422
1423
1424 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:
1425
1426 ACG GGG ATC GGG AAT TCA TCG TGA 24
1427 Thr Gly Ile Gly Asn Ser Ser
1428 1 5
1429
1430
1431 (2) INFORMATION FOR SEQ ID NO:45:

Raw Sequence Listing
Patent Application US/07/616,369

06/13/91
14:58:51

1432
1433 (i) SEQUENCE CHARACTERISTICS:
1434 (A) LENGTH: 7 amino acids
1435 (B) TYPE: amino acid
1436 (D) TOPOLOGY: linear
1437
1438 (ii) MOLECULE TYPE: protein
1439
1440 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:
1441
1442 Thr Gly Ile Gly Asn Ser Ser
1443 1 5

PAGE: 1

SEQUENCE VERIFICATION REPORT
PATENT APPLICATION US/07/616,369

DATE: 06/13/91
TIME: 14:58:51

LINE ERROR

ORIGINAL TEXT

33 Wrong application Serial Number
34 Wrong Filing Date
40 Unknown or Misplaced Identifier

OK (A) APPLICATION NUMBER: US 07/616,369
(B) FILING DATE: 21-NOV-1990
(C) CLASSIFICATION:

PAGE: 1

SEQUENCE MISSING ITEM REPORT
PATENT APPLICATION US/07/616,369

DATE: 06/13/91
TIME: 14:58:51

MANDATORY IDENTIFIER THAT WAS NOT FOUND

PAGE: 1

SEQUENCE CORRECTION REPORT
PATENT APPLICATION US/07/616,369

DATE: 06/13/91
TIME: 14:58:51

LINE ORIGINAL TEXT

CORRECTED TEXT

37 (v) PRIOR APPLICATION DATA;

(v) PRIOR APPLICATION DATA:

11/4



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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07/616,369 11/21/90 ZEBEDEE

S PHA0026

EXAMINER

WORTMAN, D

ART UNIT

PAPER NUMBER

1802

DATE MAILED:

12/17/91

DRESSLER, GOLDSMITH, SHORE,
SUTKER & MILNAMOW, LTD.
11300 SORRENTO VALLEY RD, STE 200
SAN DIEGO, CA 92121

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

Restriction/Election Only

☐ This application has been examined ☐ Responsive to communication filed on ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 30 month(s), 30 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I. THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐

Part II SUMMARY OF ACTION

1. ☒ Claims 1-53 are pending in the application.
Of the above, claims are withdrawn from consideration.
2. ☐ Claims have been cancelled.
3. ☐ Claims are allowed.
4. ☐ Claims are rejected.
5. ☐ Claims are objected to.
6. ☒ Claims 1-53 are subject to restriction or election requirement.
7. ☐ This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. filed on
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Restriction to one of the following inventions is required under 35 U.S. 121:

- I. Claims 1-14, drawn to DNA sequences, classified in Class 536, subclass 27.
- 5 II. Claims 15-27, drawn to proteins, classified in Class 530, subclass 350.
- III. Claims 35-46, drawn to an immunoassay, classified in Class 435, subclass 5.
- 10 IV. Claims 28-34, drawn to kits containing antibodies, classified in Class 435, subclass 5.
- V. Claims 47-53, drawn to vaccine and method of immunizing, classified in Class 424, subclass 89.

15 The inventions are distinct, each from the other because of the following reasons:

20 The products of Group I, II, and IV are separate, distinct products. The DNA of Group I has other uses than in the production of the product of Group II, e.g., it can be used as a probe in a hybridization assay. The product of Group II can be obtained from sources other than the invention of Group I, i.e., it can be synthesized chemically or it can be purified from natural sources.

25 The product of Group I is not required for the inventions of Group III, Group IV, or Group V.

30 Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product of Group II has
35 uses other than the method of Group III, e.g., in affinity purification.

40 Inventions II and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product of Group II has
45 uses other than the method of Group V, e.g., in the method of Group III, or in affinity purification.

50 The method of Group III does not require the invention of Group IV. The invention of Group IV can be used for other than immunoassays, e.g. the antibodies can be used in affinity

purification of viral proteins where the antigen would be useful as a standard.

5 The methods of Group III and Group V are separate, distinct methods, each requiring different method steps and different reagents.

10 Because these inventions are distinct for the reasons given above and have achieved a separate status in the art as shown by their different classifications, restriction for examination purposes as indicated is proper.

15 In addition to the restriction requirement, the following election of species requirement is applied:

This application contains claims directed to the following patentably distinct species of the claimed invention: DNA sequences and amino acid sequences.

20 Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, no claim is believed to be generic.

25 Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

30 Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

40 Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

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Serial No. 616369
Art Unit 1802

-4-

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.


Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication should be directed to Donna C. Wortman at telephone number (703) 308-3988.

20

25


Donna C. Wortman, Ph.D.
December 16, 1991


ESTHER L. KEPLINGER
SUPERVISORY PATENT EXAMINER
GROUP ART UNIT 1802



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.

Serial No.: 07/616,369

Filed: November 21, 1990

For: NON-A, NON-B HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHODS AND
VACCINES

Examiner: D. Wortman

Group Art Unit: 1802

Attorney Docket No.:
PHA-0026P

Full
127/94
9

ELECTION

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231



Sir:

In response to the Action requiring restriction mailed December 17, 1991, claim Group III (claims 35-46) is hereby elected without traverse.

The Action requests election of species for DNA sequences and amino acid sequences. Claims to neither DNA nor amino acid sequences have been elected. As a consequence, it is believed that no further election of species is required.

In the event that the request for election of an amino acid sequence recited in the Action was meant to refer to proteins that include particular sequences as are recited in elected claim 35, a protein including an amino acid residue sequence represented by the sequence shown in Figure 1 from residue 2 to residue 40 is elected. Each of the elected claims reads substantially or completely on that elected species.

It is requested that all further correspondence be addressed to the undersigned counsel at the address shown on this paper.

Respectfully submitted,

By Edward P. Gamson
Edward P. Gamson, Reg. No. 29,381

Dressler, Goldsmith, Shore,
Sutker & Milnamow, Ltd.
4700 Two Prudential Plaza
180 North Stetson Avenue
Chicago, Illinois 60601
312/616-5400

CERTIFICATE OF MAILING

I hereby certify that this communication is being deposited with the United States Postal Services as First Class Mail, postage prepaid, in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on January 15, 1992.

Edward P. Gamson



**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/616,369	11/21/90	ZEBEDEE	S PHA0026

EXAMINER
WORTMAN, D

DRESSLER, GOLDSMITH, SHORE,
SUTKER & MILNAMOW, LTD.
11300 SORRENTO VALLEY RD, STE 200
SAN DIEGO, CA 92121

ART UNIT
1802

PAPER NUMBER
10

DATE MAILED: 04/15/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152 |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims ~~1-53~~ 1-53 are pending in the application.

Of the above, claims 1-34, 47-53 are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 35-46 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Applicant's election without traverse of Group III, Claims 35-46 in Paper No. 9 is acknowledged, as is the election of amino acid sequence shown in Fig. 1 from residue 2 to residue 40. Group III has been examined and all the claimed sequences have been treated at this time.

Because of the lengthy specification in this application, it has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is therefore requested in promptly correcting any errors of which he or she may become aware in the specification or drawings.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to teach how to make and/or use the invention.

The specification is not enabling for a method of assaying a sample for the presence of antibodies against a NANBV structural antigen by mixing the sample with a NANBV protein that includes the sequences as recited. Such a protein would necessarily occur in the virion per se and Applicant has not shown how to perform such an assay with whole virions; e.g. Applicant has not shown how to isolate and purify entire virions.

Claims 35-46 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

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Art Unit 1802

-3-

Claims 37 and 38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 37 and 38 are confusing as each depends from Claim 34 and recites "The method ..." without antecedent. It is possible that Claims 37 and 38 were intended to depend from Claim 35.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 35-46 are rejected under 35 U.S.C. § 103 as being unpatentable over Kuo et al. in view of Vyas, Neurath, and

Sugahara et al. and further in view of Takeuchi et al. Kuo teaches an assay for hepatitis C virus antibodies using hepatitis C proteins but does not teach use of hepatitis C structural protein. Vyas, Neurath, and Sugahara all show use of other
5 hepatitis virus structural proteins to detect antibodies against the virus but do not teach hepatitis C virus. Takeuchi teaches the nucleotide and amino acid sequences of hepatitis C structural proteins. It would have been obvious to one of ordinary skill in the art to use the hepatitis C structural protein sequence of
10 Takeuchi to produce hepatitis virus structural proteins as in Vyas, Neurath, and Sugahara and to use them in the hepatitis C antibody assay of Kuo with reasonable expectation for success because Vyas, Neurath, and Sugahara all teach that viral
15 structural proteins contain antigenic determinants that are useful for detecting antibodies in sera of infected patients. One would have expected to be successful assaying for hepatitis C using the procedures of Vyas, Neurath, and Sugahara which have been successful for other viruses. Since the structural proteins are on the surface of the virus, one would have expected
20 antibodies to have been raised against these proteins.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the

Serial No. 616369
Art Unit 1802

-5-

Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax
Center number is (703) 308-4227.

Any inquiry concerning this communication should be directed
to Examiner Donna C. Wortman at telephone number (703) 308-1032.

5

DCW
Donna C. Wortman, Ph.D.
April 13, 1992

Esther Kepplinger
ESTHER L. KEPPLINGER
SUPERVISORY PATENT EXAMINER
GROUP ART UNIT 1802

FORM PTO-892 (REV. 3-78)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO. 616369	GROUP/ART UNIT 1802	ATTACHMENT TO PAPER NUMBER 10
NOTICE OF REFERENCES CITED		APPLICANT(S) Zebedee et al.		

U.S. PATENT DOCUMENTS						
*	DOCUMENT NO.					
	DATE					
	NAME					
	CLASS					
	SUB-CLASS					
	FILING DATE IF APPROPRIATE					
A	4415491	11/83	Vyas	436	820	
B	4591552	5/86	Neurath	435	5	
C	4839277	6/89	Sugahara et al.	435	5	
D						
E						
F						
G						
H						
I						
J						
K						

FOREIGN PATENT DOCUMENTS							
*	DOCUMENT NO.						
	DATE						
	COUNTRY						
	NAME						
	CLASS						
	SUB-CLASS						
	PERTINENT SHOTS, DWG. SPEC.						
L							
M							
N							
O							
P							
Q							

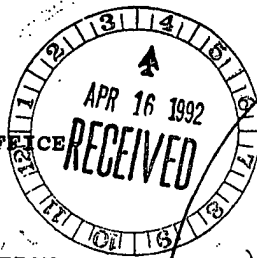
OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)	
R	Kuo et al., Science 244: 362-364. 1989.
S	Takeuchi et al., Nucl. Acids Res. 18: 4626. 1990.
T	
U	

EXAMINER Don C. Work	DATE 4/3/92
--------------------------------	-----------------------

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant: Zebedee et al.

Serial No.: 07/616,369

Filed: November 21, 1990

For: NON-A, NON-B, HEPATITIS
VIRUS ANTIGEN, DIAGNOSTIC
METHODS AND VACCINES

) PATENT APPLICATION

) Examiner: D. Wortman

) Group Art Unit: 1802

rw
4-23-92
#11

INFORMATION DISCLOSURE STATEMENT

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. §1.97, a list of documents is disclosed on the attached form PTO-1449 that may be material to the examination of this application. The subject application is one of three related applications referred to herein as the "grandparent", "parent", and "child" applications. The serial numbers and filing dates of those applications are 07/573,643 filed on August 25, 1990 (the grandparent application), 07/616,369 filed on November 21, 1990 (the subject and parent application and a C-I-P of the grandparent application), and 07/748,564 filed on August 21, 1991 (the child application and a C-I-P application of the parent application).

Listed documents A and D-N on the attached form PTO-1449 are cited and discussed in all three applications.

Listed documents O-Z are recited and discussed only in the child application.

Listed documents AA-AG are included on the list as general background art related to the work of some of the present inventors on non-A/non-B hepatitis viruses.

Listed documents B, C and AH were cited in the International Search Report for PCT Application PCT/US91/06037, which

application corresponds to the child application. A copy of that International Search Report is enclosed for the Examiner's convenience.

In accordance with 37 C.F.R. §1.98(2)(d), a copy of each of the listed documents was included with the Information Disclosure Statement filed with the grandparent application on April 10, 1992 and can be found in that application file.

No inferences should be drawn that the attached list represents a comprehensive investigation, or that any material disclosed is equivalent to the subject invention. In addition, none of the documents that have publication dates prior to the priority date of the above application anticipate the invention in this application.

The cited documents disclose numerous specific features. There has been no attempt to list each and every feature disclosed by each document. The Examiner is requested to review the documents and determine the extent of the materiality of the document disclosures with respect to the present invention.

The recitation of any art or any document herein is not to be construed as an admission that the art or document disclosure is necessarily within the invention field of endeavor, that the art or document disclosure is necessarily prior in time to a particular date which may be relevant to the instant patent application, and/or that the art or document disclosure is otherwise necessarily prior art as defined by the patent law with respect to the instant invention and application.

Also, there is reserved the right to later set forth how the instant invention is distinguished over the disclosure of any document or other art, including the disclosures of the art and documents recited herein, that may be cited by the Examiner in rejecting a claim in the instant patent application.

07/616,369

-3-

The recitation herein of the art and documents is not to be construed as an assertion that more pertinent art could not possibly be in existence.

Respectfully submitted,

By Edward P. Gamson
Edward P. Gamson, Reg. No. 29,381

Enclosures

1. Form PTO-1449 and;
2. A copy of the International Search Report for PCT Application PCT/US91/06037, which corresponds to U.S. Patent Application S/N 07/748,564

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CERTIFICATION OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on April 10, 1992.

Edward P. Gamson
Edward P. Gamson

Attorney Docket No.
PHA-0026

Serial No. 072616.369

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

Applicant
Zebedee et al.

Filing Date
November 21, 1990

APR 16 1992

Group
1802

U.S. PATENT DOCUMENTS

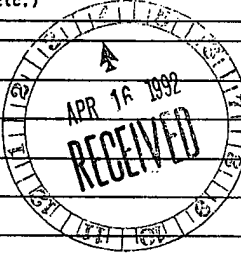
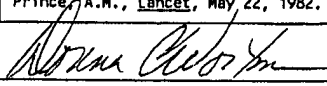
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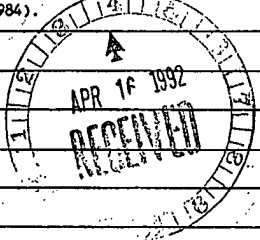
D	Choo et al, <u>Science</u> , <u>244</u> , 359-362 (1989)
E	Okamoto et al, <u>Japan J. Exp. Med.</u> , <u>60</u> , 163-177 (1990)
F	Miller et al., <u>PNAS</u> <u>87</u> , 2057-2061 (1990)
G	Kuo et al, <u>Science</u> <u>244</u>, 362-364 (1989) cited in paper
H	Alter et al, <u>NEJM</u> <u>321</u> , 1538-39 (1989)

Examiner

Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 Rev. 3-88)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. PHA-0026		Serial No. 07/616,369	
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)				Applicant Zebedee et al.			
				Filing Date November 21, 1990			
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)							
I	Alter et al, <u>NEJM</u> , 321, 1494-1500 (1989)						
J	Weiner et al, <u>Lancet</u> , 335, 1-3 (1990)						
K	McFarlane et al, <u>Lancet</u> , 335, 754-757 (1990)						
L	Grey et al, <u>Lancet</u> , 335, 609-610 (1990)						
N	Houghton et al, <u>Int. K. Prot Res</u> , 16, 311-320 (1980)						
O	Choo et al, <u>PNAS</u> , 88, 2451-2455 (1991)						
P	Takamizawa et al., <u>J. Virol.</u> , 65, 1105-1113 (1991)						
Q	Kato et al, <u>PNAS</u> , 87, 9524-9528 (1990)						
R	Takeuchi et al, <u>Nucleic Acids Res.</u>, 18, 4626 (1990) cited on PTO doc						
S	Ogata et al, <u>PNAS</u> , 88, 3392-3396 (1991)						
T	Han et al., <u>PNAS</u> , 88, 1711-1715 (1991)						
U	Meyer et al., <u>Virol</u> , 171, 555-567 (1989)						
V	Collett et al., <u>Virol</u> , 165, 191-199 (1988)						
W	Brinton et al., <u>Virol</u> , 162, 290-299 (1988)						
X	Inchauspe et al, <u>PNAS</u> , 88, 10292-10296 (1991)						
Y	Wiener et al, <u>Virol</u> , 180, 842-848 (1991)						
Z	Hahn et al, <u>Virol</u> , 162, 167-180 (1988)						
AA	Prince et al, <u>Lancet</u> , 2:241 (1974)						
AB	Prince et al., "Posttransfusion Viral Hepatitis Caused by an Agent or Agents Other Than Hepatitis B Virus or Hepatitis A Virus. Impact On Efficiency of Present Screening Methods." in <u>Transmissible Disease & Blood Transfusion</u> , Tibor et al. eds., Grune & Stratton, Inc., pp. 129-140 (1975)						
AC	Prince et al., "Non-A/Non-B Hepatitis: Identification of a virus-specific antigen and antibody. A preliminary report" in <u>Viral Hepatitis</u> , Vyas et al., eds., Franklin Institute Press, Philadelphia, Pa. pp. 633-640 (1978).						
AD	Prince et al., "Non-A, Non-B Hepatitis: Reproduction of disease in chimpanzees and identification of virus specific antigen and antibody" in <u>Transplantation and Clinical Immunology</u> , Volume X, Touraine et al., eds., Excerpta Medica, Amsterdam, pp. 8-17 (1979).						
AE	Prince, A.M., <u>Lancet</u> , May 22, 1982.						
Examiner 				Date Considered 9/22/92			
*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.							

Form PTO-1449 (Rev. 9-88)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. PHA-0026	Serial No. 07/616,369
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)		Applicant Zebedes et al.	
		Filing Date November 21, 1990	Group 1802
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)			
AF	Prince et al., "Use of liver cell cultures in studies on the replication of hepatitis and non-A, non-B viruses in Viral Hepatitis and Liver Disease," Grimes & Stratton, pp. 459-464 (1984).		
AG	Brotman et al., <u>J. Infect. Diseases</u> , 151(4):618 (1985)		
AH	Takeuchi, et al. <u>Gene</u> , 91:287 (1990)		
<div style="text-align: right;">  </div>			
Examiner	Date Considered		
<i>David C. ...</i>	<i>9/22/92</i>		
<p>*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>			

PATENT COOPERATION TREATY

New York Blood Center
Office of Patents & Licenses
310 East 67th St.
New York, N.Y.
10021

EP 2/4192
FEB 8 1992
UNITED STATES
INTERNATIONAL SEARCHING AUTHORITY
NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL SEARCH REPORT
OR THE DECLARATION
Issued pursuant to PCT Rule 44.1

*packaged
for 2/4/92
MSB*

DATE OF MAILING by the International Searching Authority **24 JAN 1992**

Inscribe NAME and ADDRESS of the AGENT and if there is no agent, of the APPLICANT

APPLICANT'S OR AGENT'S FILE REFERENCE
PHA 0029

IDENTIFICATION OF THE INTERNATIONAL APPLICATION

International Application No.

PCT/US91/06037

International Filing Date

23 August 1991

Applicant(Name)

New York Blood Center

NOTIFICATION

The applicant is hereby notified that, in regard to the above-identified international application, this International Searching Authority transmits herewith:

1. ☒ the international search report.

THE ATTENTION OF THE APPLICANT IS DRAWN TO THE TIME LIMIT FOR AMENDING BEFORE THE INTERNATIONAL BUREAU ACCORDING TO ARTICLE 19(1) AND RULE 46.1 WHICH RUNS FROM THE DATE OF MAILING OF THE INTERNATIONAL SEARCH REPORT

2. ☐ the declaration to the effect that no international search report will be established.

THE ATTENTION OF THE APPLICANT IS DRAWN TO THE TIME LIMIT FOR COMPLYING WITH THE REQUIREMENTS OF ARTICLE 22(2).

☐ Applicant is further notified that, the protest against payment of an additional fee under Rule 40.2(c) together with the decision thereon has been transmitted to the International Bureau together with the request to forward the texts of both the protest and the decision thereon to designated Offices.

THE UNITED STATES INTERNATIONAL SEARCHING AUTHORITY

Address only:
Commissioner of Patents and Trademarks
Box PCT
Washington, D. C. 20231

Authorized Officer

Donna Wortman

Attn: ISA/US

Attn: ISA/US

PATENT COOPERATION TREATY INTERNATIONAL SEARCH REPORT

IDENTIFICATION OF INTERNATIONAL APPLICATION		Applicant's or Agent's File Reference PHA 0029
International Application No. PCT/US91/06037	International Filing Date 23 August 1991	
Receiving Office RO/US	Priority Date Claimed 25 August 1990	
Applicant New York Blood Center		
I. <input type="checkbox"/> CERTAIN CLAIMS WERE FOUND UNSEARCHABLE : (Observations on supplemental sheet (2))		
II. <input type="checkbox"/> UNITY OF INVENTION IS LACKING : (Observations on supplemental sheet (2))		
III. TITLE, ABSTRACT AND FIGURE OF DRAWING		
1. The following indicated items are approved as submitted by the applicant: : <input checked="" type="checkbox"/> Title. <input checked="" type="checkbox"/> Abstract.		
2. The texts established by this International Searching Authority of the following indicated items are set forth below: <input type="checkbox"/> Title. <input type="checkbox"/> Abstract.		
<p style="margin-top: 20px;">Text of the abstract continued on supplemental sheet</p> <p>3. a. <input type="checkbox"/> The definitive contents of the abstract are established by this International Searching Authority as proposed in form PCT/ISA/204 previously sent to the applicant. b. <input type="checkbox"/> This report is incomplete as far as the abstract is concerned as the time limit for comments by the applicant on the draft prepared by this International Searching Authority has not expired</p> <p>4. Figure to be published with the abstract <input type="checkbox"/> None of the figures. Figure No. _____ <input checked="" type="checkbox"/> as suggested by the applicant <input type="checkbox"/> as suggested by the applicant <input type="checkbox"/> because the applicant failed to suggest a figure <input type="checkbox"/> because the applicant failed to suggest a figure <input type="checkbox"/> because this figure better characterizes the invention <input type="checkbox"/> because this figure better characterizes the invention </p>		

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/06037

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC U.S. CL.: 536/27; 530/350, 387; 435/5; 424/89 IPC(5): C07H 15/12; C07K 3/00; C12Q 1/70; A61K 39/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
U.S.	536/27; 530/350, 387; 435/5; 424/89	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
STIC Sequence Search APS		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	Gene, Volume 91, issued 1990, K. Takeuchi et al., "Hepatitis C viral cDNA isolated from a healthy carrier donor implicated in post-transfusion non-A, non-B hepatitis," pages 287-291, see entire document.	1,3-6
X Y	EP, A, 0,318,216 (Houghton et al.) 31 May 1989, see figures and claims.	16 3-15,17-45
X Y,P	EP, A, 0,388,232 (Houghton et al.) 19 September 1990, see figures and claims.	16 1-15,17-45
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
07 January 1992	24 JAN 1992	
International Searching Authority	Signature of Authorized Officer	
ISA/US	Donna C. Wortman	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . . because they relate to subject matter^{1,2} not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out^{1,2}, specifically:

3. ☐ Claim numbers . . . because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING³

This International Searching Authority found multiple inventions in this international application as follows:

See attached sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application. Telephone practice

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.



12
57.1/92
001
Atty. Docket PHA0026

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

M.A.
7/31/92
Applicant: Zebedee et al.

Serial No.: 07/616,369

Filed: November 21, 1990

For: NON-A, NON-B, HEPATITIS
VIRUS ANTIGEN, DIAGNOSTIC
METHODS AND VACCINES

) PATENT APPLICATION

) Examiner: D. Wortman

) Group Art Unit: 1802

112/B
D. Wortman
7/30/92
RECEIVED

JUL 27 1992

GROUP 1800

AMENDMENT UNDER 37 C.F.R. § 1.115

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

This Amendment is being filed in response to the April 15, 1992 Office Action (paper no. 10) issued in connection with the above-captioned patent application.

IN THE CLAIMS:

Please cancel claims 1-34 and 47-53 without prejudice to their being represented in a divisional application.

35. (Amended) A method of assaying a body fluid sample for the presence of antibodies against [a] NANBV [structural antigen], which method comprises:

Bgbc
a) forming an immunoreaction admixture by admixing said body fluid sample with a recombinant NANBV structural protein or synthetic polypeptide portion thereof, said recombinant protein or polypeptide including an amino acid residue sequence represented by the sequence contained in SEQ. ID NO. 1 from residue 1 to residue 20, from residue 21 to residue 40, or from residue 2 to residue 40;

b) maintaining said immunoreaction admixture for a time period sufficient for any of said antibodies present to

immunoreact with said recombinant NANBV structural protein or synthetic polypeptide to form an immunoreaction product; and

c) detecting the presence of any of said immunoreaction product formed and thereby the presence of said antibodies.

In claim 37, delete the phrase "Claim 34" and replace it with the phrase --claim 35--. In addition, insert the word --recombinant-- before the word "NANBV".

In claim 38, delete the phrase "claim 34" and replace it with the phrase --claim 35--. In addition, insert the word --recombinant-- before the word "NANBV".

In claim 39, insert the word --recombinant-- before the word "NANBV".

IN THE SPECIFICATION:

At page 2, line 36, please delete "theviral", and replace it with --the viral--.

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the discussion that follows is respectfully requested.

In claims 1-34 and 47-53 have been cancelled in view of the restriction requirement and without prejudice to their being presented again in a divisional application. Claims 35-39 have been amended. Claims 35-46 are before the Examiner.

I. THE AMENDMENTS

Support for the addition of the words "recombinant" and "synthetic polypeptide" to claims 35-39 can be found in the

specification at least at page 19, line 7 to page 21, line 22. Those pages of the specification set forth methods for making a recombinant structural protein and synthetic polypeptide of the present invention.

Exemplary use of a method of the invention can be found at least at page 69, line 28 through page 76, line 12. Those pages of the specification exemplify the use of a recombinant NANBV structural protein in an assay for the detection of antibodies against NANBV.

Claims 37 and 38 have been amended to correct inadvertent errors in dependency to make those claims dependent upon claim 35 instead of claim 34. The Examiner is thanked for noting the errors.

The specification has been amended at page to correct a minor typographical error.

II. Rejection Under 35 U.S.C. § 112, First And Second Paragraphs

A. First Paragraph

The Action has objected to the specification under 35 U.S.C., Section 112, first paragraph as failing to provide an adequate written description of the invention and as failing to teach how to make and use the invention. The Action has rejected claims 35 and 46 under 35 U.S.C. § 112, first paragraph for the reason set forth in the objection to the specification. In particular, the Action asserts that the specification is not enabling for a method of assaying a body fluid sample for the presence of antibody against a NANBV structural antigen by mixing the sample with a NANBV structural protein because such a protein would necessary occur in the virion and that Applicant has not shown how to perform such an assay.

In view of the clarifying amendments to claim 35, this rejection should be moot. Thus, a recombinant protein or a synthetic polypeptide portion thereof would not be present in a virion.

B. Second Paragraph

Claims 37 and 38 were rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point-out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Action asserts that the use of phrase "The method" in claims 37 and 38 is without antecedent basis from claim 34. In view of the amendments to claims 37 and 38, this rejection should be moot.

III. Rejection Under 35 U.S.C. § 103

The Action has rejected claims 35-46 under 35 U.S.C §103 as being unpatentable over Kuo et al., (hereinafter referred to as "Kuo") in view of Vyas, Neurath, and Sugahara et al. (hereinafter referred to as "Sugahara") and further in view of Takeuchi et al. (hereinafter referred to "Takeuchi"). The Action characterizes:

- 1) Kuo as teaching assays for hepatitis C virus antibodies using hepatitis C proteins, but not using hepatitis C structural proteins;
- 2) Vyas, Neurath and Sugahara as teaching the use of hepatitis B virus structural proteins to detect antibodies against the virus, but not teaching use of hepatitis C virus proteins; and
- 3) Takeuchi as teaching the nucleotide and amino acid sequence of hepatitis C structural proteins.

In view of that characterization, the Action concludes that it would have been obvious to one of ordinary skill in the art to

use the hepatitis C structural protein sequence of Takeuchi to produce hepatitis viral structural proteins as in Vyas, Neurath and Sugahara and to use those proteins in the hepatitis C antibody assay of Kuo with reasonable expectation of success. In support of that conclusion, the Action further asserts that because Vyas, Neurath and Sugahara all teach that viral structural proteins contain antigenic determinants that are useful in detecting antibodies in sera of infected patients, one would have expected to be successful in assaying for hepatitis C using those proteins. The Action still further states that because the structural proteins are on the surface of the virus, one would have expected antibodies to have been raised against those proteins.

That rejection by the Action is respectfully traversed on the bases that (1) the Action has credited the cited art with teachings not contained therein, (2) the art is not properly combineable and (3) even if combined, those combined teachings fall short of describing the present invention.

A. First Basis

First, the Action characterizes Kuo as teaching assays for antibodies against hepatitis C virus using hepatitis C proteins, but not structural proteins. It is respectfully submitted that the teaching of Kuo is more narrow than indicated by the Action.

Kuo actually teaches an assay for antibodies against hepatitis C virus using a single fusion protein comprising 363 viral amino acid residues of non-structural protein. As noted in the large paragraph at page 3 of the specification, the Kuo construct is a fusion protein containing products of two non-structural protein genes.

Second, the Action credits Vyas, Neurath and Sugahara with teaching that hepatitis B structural proteins have use in an assay for detecting antibodies against the virus. It is submitted that the Vyas, Neurath and Sugahara teachings, all of which relate to hepatitis B viral surface and core proteins, are not relevant here, and that those teachings should be withdrawn.

As is pointed out in the specification at page 2, beginning at line 18, the NANBV genome is comprised of a single, plus strand of RNA that encodes a single polyprotein. The hepatitis B virus (HBV) genome is double-stranded circular DNA. Hepatitis B virus belongs to a novel class of enveloped hepatropic DNA viruses, the hepadnavirus family (see Exhibit A, attached hereto). Document F of the recently filed Information Disclosure Statement points out that NANBV has similarities to the animal pestiviruses and plant carmovirus and polyvirus.

Thus, except for the facts that both are viruses and both NANBV and HBV infect the liver and cause inflammation (hepatitis), the two viruses have little in common. That being the case, it is submitted to be improper to draw any conclusion as to any other similarity of properties between the two viruses, let alone antigenicity or immunogenicity of proteins from the two viruses.

The Takeuchi teaching provides a naked DNA sequence and putative amino acid residue sequence in which the core and envelope regions of the fusion protein are putatively assigned. No mention is made of any encoded region that might have use in an assay for anti-HCV antibodies.

In view of the above, it is respectfully submitted that the Action has credited the cited art with teachings not disclosed therein.

B. Second Basis

To establish a prima facie case of obviousness based on a combination of teachings, 1) the teachings themselves must suggest the combination or 2) there must be a compelling motivation to combine the teachings, which motivation is based on sound scientific principles. Ex parte Kranz, 19 USPQ2d 1218 (Bd. Pat. App. Inter. 1991).

1. Art-based suggestion to combine

As set forth above, Kuo teaches an assay for antibodies against hepatitis C virus using a single fusion protein comprising 363 viral amino acid residues. Kuo neither mentions nor suggests that structural proteins or portions thereof can be used in his assay. In addition, Kuo fails to even mention any other virus, let alone another hepatitis virus. Kuo, therefore, cannot be viewed as suggesting the combination proposed by the Action.

The suggestion for combination is not provided by Vyas, Neurath or Sugahara. None of that cited art discloses peptides or assays for detecting antibodies against a virus other than HBV, a virus already shown to be quite different. Further, none of that art relates to hepatitis C. Still further, Vyas and Neurath teach use of peptides to a surface structural protein, HbsAg, whereas the sequences claimed here relate to the capsid. It is submitted that no properly suggestive inference can be drawn from results with the surface protein to results with the capsid protein of an entirely different virus. Reliance on Vyas and Neurath should therefore be withdrawn.

Although Takeuchi discloses the nucleic acid and derived amino acid residue sequences of HCV structural proteins, Takeuchi does not teach the location or identity of any antigenic determinants that might have use in designing an assay for

detection of antibodies against HCV as claimed herein. In view of the above, it is respectfully submitted that the cited art cannot provide the requisite motivation for combination as proposed by the Action, and this rejection should be withdrawn.

2. Compelling motivation based on sound scientific principles

There is no compelling motivation based on sound scientific principles to combine the art cited by the Action. First, the teachings of Vyas, Neurath and Sugahara relate to hepatitis B virus. Those teachings have application to the teachings of Kuo and Takeuchi (related to hepatitis C virus) only if there is a known relationship between those viruses. The Action provides no evidence to support such a relationship.

To the contrary, the art relied upon by the Action and that provided earlier shows that hepatitis B and C differ substantially in structure. Further, the art points out that major differences between those viruses occur in genomic coding and protein expression of antigens, the very portions of the virus giving rise to the Action's reliance.

Vyas and Neurath disclose peptides associated with the hepatitis B surface antigen. That antigen is known to be expressed on the outer covering of the hepatitis B virus (See the article from Laboratory Investigation enclosed herewith as Exhibit A).

Notably absent from the teachings of Kuo is any mention whatsoever of a surface antigen encoded by a hepatitis C genome or expressed by that virus. Even if there were such a teaching, it would not be relevant as the sequences claimed herein are from the capsid.

It can thus be seen that none of the cited art provides any guidance on what part, if any, of the hepatitis C genome or

proteins expressed therefrom might have any use. Even if one of ordinary skill in the art were motivated to combine the cited art, such an artisan would be unable to do so. There is simply no teaching anywhere in the art of record to make or use proteinaceous material having the amino acid residue sequence claimed.

Second, the Action-cited art combination also seems to be predicated on the assumption that, because short peptides that mimic portions of structural antigens have been shown to immunoreact with antibodies against intact antigens, a worker skilled in the art would have a reasonable expectation of success in there substantially always being such interactions. Not only does the Action fail to provide any evidence in support of that assumption, but there is evidence to support exactly the contrary.

Enclosed herewith as Exhibit B is an article from Science discussing antibody-protein interaction. The Examiner's attention is respectfully directed to the second full paragraph of page 662 of that article that begins near the bottom of the page. That paragraph points out that although short peptides can be used to prepare anti-protein antibodies, it is a rare event for a short peptide to be antigenic (i.e., immunoreact with antibodies against the intact protein). In view of that teaching, one of ordinary skill in the art would not be motivated to look for small linear peptides as a means for detecting antibodies against intact viruses.

It is therefore respectfully submitted that there is no compelling motivation based on sound scientific principles to combine the cited art in the manner proposed by the Action. When taken together with the absence of any art-based motivation for such a combination, it is further respectfully submitted that the

art relied upon by the Action is not properly combineable, and this rejection should be withdrawn.

C. Third Basis

Even assuming arguendo, however, that the Action-proposed combination of art were proper, such a combination falls short of describing the present invention.

The present invention relates to an assay for antibodies against NANBV using a NANBV structural protein that includes small amino acid residue sequences (up to about 39 amino acid residues) from the putative capsid antigen of NANBV (residues 1-20, 21-40 or 2-40 of SEQ ID NO:1). The structural protein can be a fusion protein (claims 36-38) that contains those same small residue sequences.

The assay of Kuo, as admitted by the Action, does not employ a NANBV structural protein. The teachings of Vyas, Neurath and Sugahara cannot provide that structural protein for at least two reasons. First, the peptides disclosed in that art are derived from HBV, not NANBV. Second, there is no basis in the record to conclude that all viral structural proteins are immunogenic or antigenic, nor that the particular regions of NANBV here claimed would be antigenic. Because Takeuchi does not even discuss antigenic determinants, his disclosure adds nothing to Kuo to provide the worker of ordinary skill with the required reasonable expectation of success. In Re O'Farrell, 7 USPQ 1673, 1681 (Fed. Cir. 1988).

In light of the reasons set forth above, it is respectfully requested that the rejection of claims 35-46 under 35 U.S.C §103 be withdrawn.

D. Enhanced Results

The Examiner's attention is also invited to the results obtained using a claimed method that are provided at page 69, line 28 through page 76, line 19. The results shown in head-to-head comparisons of the Kuo construct in a commercial Kit (Anti HCV) and an assay of this invention (Anti Cap-N, Tables 2-6 and Table 7) illustrate that an assay using a claimed method provided enhanced results as compared to the Kuo construct. Thus, an assay of the present invention was able to detect HCV infection one or more months earlier than could an assay using the Kuo construct. Those results were thoroughly unpredictable, and illustrate the non-obviousness of this invention.

Summary

Claims 1-34 and 47-53 have been cancelled and claims 35-39 amended. Each of the bases for objection or rejections have been dealt with and make moot or otherwise overcome.

In view of the amendments to the claims and for the foregoing reasons, it is respectfully submitted that the claims now stand in a condition of allowance. Early notification to that effect is respectfully requested.

Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381

Enclosures

1. Exhibits A-B and;
2. Form PTO-1449


DRESSLER, GOLDSMITH, SHORE,
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180 N. Stetson
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(312) 616-5400

07/616,369

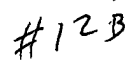
-12-

CERTIFICATION OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on July 15, 1992.



Edward P. Gamson



Sheet 1 of 1

[illegible]



md
**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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07/616,369 11/21/90 ZEBEDEE

S PHA0026

EXAMINER

WORTMAN, D

ART UNIT PAPER NUMBER

1802

13

DATE MAILED: 10/05/92

DRESSLER, GOLDSMITH, SHORE,
SUTKER & MILNAMOW, LTD.
11300 SORRENTO VALLEY RD, STE 200
SAN DIEGO, CA 92121

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 7/20/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 8 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- ☒ Notice of References Cited by Examiner, PTO-892.
- ☐ Notice re Patent Drawing, PTO-948.
- ☒ Notice of Art Cited by Applicant, PTO-1449.
- ☐ Notice of Informal Patent Application, Form PTO-152.
- ☐ Information on How to Effect Drawing Changes, PTO-1474.
- ☐

Part II SUMMARY OF ACTION

1. ☒ Claims 35-46 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-34 and 47-53 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 35-46 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Serial No. 616369
Art Unit 1802

-2-

Claims 35-46 are under examination at this time, Claims 1-34 and 47-53 having been cancelled in Paper No. 12. Claims 35, 37, 38, and 39 have been amended.

5 Claims 36-38 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter
10 which applicant regards as the invention. Claims 36-38 are unclear because each recites "... protein has an amino acid residue sequence contained in ..." and it cannot be determined from that language whether Applicant intends to claim the entire portion of the sequence that is derived from NANBV or some
15 portion of it. As recited, the claim encompasses just two adjacent amino acid residues which would constitute a sequence. In addition, the specification is not enabling for portions of the NANBV sequence since no guidance is given for selecting smaller peptides for use in the instant method.

20 The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

25 A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

30 (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

35 (c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

40 The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

45 A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

5 matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10 Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

15 This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out
20 the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 35 and 36 are rejected under 35 U.S.C. § 102(e) as
25 being anticipated by the patent to Wang. Wang teaches assaying sera for antibodies against HCV (NANBV) using solid phase coated with synthetic peptides that include amino acid residue sequences as instantly claimed (see Wang, Example 14 and Table 7, especially peptide VIIIE). It is noted that "including" as
30 recited in Claim 35 and "has" as recited in Claim 36 encompass any common amino acid sequence. Even if the instant sequences were recited more narrowly, they would have been obvious over Wang because the results represented in Table 7 clearly show immunoreactivity decreasing as the amino acid sequences between 1
35 and 40 are deleted (see Table 7, column labeled "%

Immunoreactivity," especially results obtained with peptides
VIII E, VIII D, VIII C, VIII B, VIII A).

Claims 37-46 are rejected under 35 U.S.C. § 103 as being
unpatentable over Wang in view of Kuo et al. Wang teaches the
5 HCV peptide sequences and assays discussed above but does not
teach producing the peptides recombinantly. Kuo teaches
production of an HCV recombinant fusion protein for use in
immunoassays. It would have been obvious to one of ordinary
skill in the art to produce the HCV peptide of Wang recombinantly
10 as taught by Kuo in order to gain the advantages of producing
peptides by recombinant means, e.g., to obtain a stable,
plentiful supply of peptides that are free of contamination with
other HCV antigens and to use them in immunoassays because both
Kuo and Wang successfully use HCV peptides to detect antibodies
15 in sera. With regard to Claims 41, 43, 44, and 46, Wang and Kuo
do not explicitly teach protein A for binding to immunoglobulin
nor specifically describe lanthanide chelate, biotin, or
radioactive isotopes as labels. These variations are well known
in the art and it would have been obvious to one of ordinary
20 skill in the art to substitute them for the anti-human
immunoglobulin antibody and the enzyme label of Wang with
reasonable expectation for success because they are well known
and conventionally used in immunoassays.

Because this action contains new grounds of rejection, it is
25 made non-final. Any resulting inconvenience is regretted.

Serial No. 616369
Art Unit 1802

-5-

Applicant's arguments with respect to claims 35-46 in Paper No. 12 have been considered but are deemed to be moot in view of the new grounds of rejection.

Papers related to this application may be submitted to Group 5 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

10 Any inquiry concerning this communication should be directed to Examiner Donna C. Wortman at telephone number (703) 308-1032.

15 *Don*
Donna C. Wortman, Ph.D.
September 27, 1992

Esther Kepplinger
ESTHER L. KEPPLINGER
SUPERVISORY PATENT EXAMINER
GROUP ART UNIT 1802

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NO. 616369	GROUP/ART UNIT 1802	ATTACHMENT TO PAPER NUMBER 13
NOTICE OF REFERENCES CITED				APPLICANT(S) Zebedee et al.		

U.S. PATENT DOCUMENTS																	
•	A	B	C	D	E	F	G	H	I	J	K	DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
												5106726	4-1992	Wang	435	5	7-1990

FOREIGN PATENT DOCUMENTS														
•	L	M	N	O	P	Q	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG.	PP. SPEC.

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)	
R	
S	
T	
U	

EXAMINER Ronan C. Woods	DATE 9/25/92
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* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

#14
L.P.
2-12-93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 07/616,369) Attorney Docket
) PHA-0026P
Filed: November 21, 1990) Group Art Unit: 1802
)
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: D. Wortman)

PETITION UNDER 37 C.F.R. §1.17

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

A one-month extension of time to respond to the Office
Action mailed October 5, 1992 is respectfully requested.

There is submitted herewith the following:

1. Response;
2. Declaration of Alfred M. Prince, M.D.;
3. Form PTO-1449;
4. Documents BA through BE; and
5. Check No. 19287 in the amount of the required fee .

of \$110.00 for a one-month extension of time (a response to the
Office Action was due on January 5, 1993).

The Commissioner is hereby authorized to charge payment
of any additional fees under 37 C.F.R. §1.17 to cover the cost of
the extension or credit any overpayment to Deposit Account No.
04-1644. A duplicate copy of this paper is enclosed.

Respectfully submitted,

By Edward P. Gamson
Edward P. Gamson, Reg. No. 29,381

Serial No. 07/616,369

-2-

DRESSLER, GOLDSMITH, SHORE,
SUTKER & MILNAMOW, LTD.
4700 Two Prudential Plaza
180 North Statson Avenue
Chicago, Illinois 60601
312/616-5400

CERTIFICATE OF MAILING

I hereby certify that this Petition, in duplicate, together with the aforementioned enclosures is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 28, 1993.



Edward P. Gamson

DRESSLER, GOLDSMITH, SHORE
SUTKER AND MILNAMOW, LTD.
180 N. STETSON AVENUE
CHICAGO, ILL. 60601

19287

2-91/710

PAY
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ORDER OF

COMMISSIONER OF PATENTS AND TRADEMARKS

1/28 1993 \$110.00

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PHA-0026P

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THE UNITED STATES PATENT OFFICE IS REQUESTED TO IMPRESS
ITS STAMP ON THIS CARD AND PLACE SAME IN THE OUT-GOING
MAIL TO SHOW THE FOLLOWING PAPERS HAVE BEEN RECEIVED.

Applicants: Zebedee et al.
Serial No.: 07/616,369
Group: 1802

Enclosed: AMENDMENT, certified mailed January 28, 1993,
together with copy of Declaration of Alfred
M. Price, M.D.; Form PTO-1449; Documents
BA through BE; Check No. 19287 in the amount of
\$110.00 for a one-month extension of time; and
Petition for a one-month extension of time,
in duplicate, certified mailed January 28, 1993

180
1/18/93
15
2-12-
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

MD
2/12/93
Applicant: Zebedee et al.)
Serial No.: 07/616,369) Attorney Docket
) PHA-0026P
Filed: November 21, 1990) Group Art Unit: 1802
)
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: D. Wortman)

AMENDMENT UNDER 37. C.F.R. §1.115

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In response to the Official Action dated October 5,
1992, for which a Petition for an extension of time and its
required fee are enclosed, please amend the above-identified
application as follows.

IN THE SPECIFICATION

At page 73, line 36, please delete "seraconversion",
and replace it with --seroconversion--.

IN THE CLAIMS

Please amend claims 35 and 37 as follows:

35. (Twice Amended) A method of assaying a body fluid
sample for the presence of antibodies against NANBV, which method
comprises:

DI
EX
a) forming an immunoreaction admixture by
admixing said body fluid sample with a recombinant NANBV
structural protein or [synthetic polypeptide] portion thereof,
said recombinant protein or [polypeptide] portion including an
amino acid residue sequence represented by the sequence contained
in SEQ. ID NO. 1 [from residue 1 to residue 20,] from residue 21
to residue 40[, or from residue 2 to residue 40];

DI
Revised
b) maintaining said immunoreaction admixture for a time period sufficient for any of said antibodies present to immunoreact with said recombinant NANBV structural protein or [synthetic polypeptide] portion to form an immunoreaction product; and

c) detecting the presence of any of said immunoreaction product formed and thereby the presence of said antibodies.

In claim 37, line 1, please insert the word --recombinant-- before the word "NANBV".

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the discussion that follows is respectfully requested.

Claims 35 and 37 have been amended as discussed below. Claims 35-46 are before the Examiner.

I. The Amendments

A typographical error has been corrected at page 73, line 36.

Claims 35 and and all of its dependent claims (36-46) have been amended to recite only recombinantly produced particular NANBV proteins or portions thereof, with references to "synthetic" polypeptide portions being deleted. The use of recombinant proteins and portions is discussed throughout the specification and is exemplified in the working examples, as will be discussed hereinafter.

Claim 35 and its dependent claims have also been amended to recite only a recombinant that (includes) the sequence of SEQ. ID. No. 1 from residue 21 through residue 40. Such recombinant molecules are discussed in the prior claim as well as throughout the application and include those recombinant antigens

referred to as CAP-N (residues 1-74), CAP-B (residues 20-41) and the entire capsid (residues 1-120). See for example, Tables 2-7 and the text at pages 53-76.

It is thus seen that no new matter has been added.

II. The Action

A. Rejection Under 35 U.S.C. §112, First and Second Paragraphs

Claims 36-38 were rejected as allegedly lacking enablement and being indefinite for their use of the language "protein has the amino acid residue sequence contained in ...". The Action continued by saying "it cannot be determined from that language whether Applicant intends to claim the entire portion of that sequence that is derived from NANBV or some portion of it." The Action asserted that the claim language reads upon a sequence containing "just two adjacent amino acid residues ...", and that there is insufficient enablement for selecting smaller portions for use in the instant method.

This rejection is respectfully traversed.

It is respectfully submitted that the phrase quoted above and in the Action has been taken out of context, and that it is that out-of-context reading that has led to the present rejections. It is thus submitted that the proper interpretation that should be given to the quoted phrase and its surrounding context of the original and amended claims 36-38 is that the entire recited sequence of each claim is to be present.

It is noted that claim 35 contained similar language that was not the basis of the subject rejection, or another rejection. That language of claim 35 recited an "amino acid residue sequence represented by the sequence contained in SEQ. ID. NO. ..." If the Examiner is unpersuaded by the comments above and is of the view that the language quoted from claim 35

in this paragraph is more apt and would avoid this rejection, the quoted language of this paragraph may be added by Examiner's amendment after a conference with counsel. If a more formal amendment process is required, counsel will be pleased to submit such an amendment.

B. Rejection Under 35 U.S.C. §102(e)

Claims 35 and 36 were rejected as above based on the U.S. patent to Wang. The Action noted that "Wang teaches assaying sera for antibodies against HCV (NANBV) using [a] solid phase coated with synthetic peptides that include amino acid sequences instantly claimed ..." Wang's Example 14 and Table 7 were particularly relied-on, and especially her peptide VIIIE. This portion of the Action concluded with a statement to the effect that even if the claimed sequences were recited more narrowly than the "including" language of claim 35 and the "has" language of claim 36 makes them, the method would still be obvious over Wang's teachings because of the similarity of the sequences involved.

This rejection is respectfully traversed for the reasons discussed below.

Before going further, it must be reiterated that the present claims relate to recombinantly produced proteins or portions thereof, whereas Wang teaches the use of synthetically produced polypeptides. Wang teaches at column 24, lines 14-19 that her peptides "were synthesized by the 'classical' Merrifield method of solid phase peptide synthesis using side chain protected t-Boc-amino acids ..."

Although one, a priori, might not think that there would be a difference in an assay result between the use of a chemically synthesized peptide of Wang and a recombinantly prepared similar amino acid residue sequence, the data of the

present application, that provided in the accompanying Declaration and that relied-on in the Action show that there is a difference between the chemically prepared and recombinantly prepared materials where the presently claimed assays are concerned. The reason for this difference in result is unknown.

Although the observed difference between a chemically synthesized peptide and a similar recombinantly produced sequence could not be predicted a priori, the Wang patent itself contains a similar situation with two chemically produced peptides. Thus, the sequence EECSQHLPYI is present in both of Wang's peptides I and III. In peptide I, that sequence is shown as being a strong contributor to immunoreaction, whereas in peptide III, the same sequence fails to bind antibodies. See, Wang's Fig. 1-4.

Thus, Wang teaches that the same sequence in two different environments can produce different and unpredictable antibody binding results. The same has been found here in comparing a synthetic peptide to a recombinantly produced protein or portion.

Turning now to the Wang teachings, the Examiner's attention is invited to column 41, lines 45 and 46 of Wang wherein it is stated that the relative percentages of immunoreactivity of Table 7 are related to results obtained with peptide IIID. Wang's Table 1 shows that a relative immunoreactivity of peptide IIID was set at an apparently arbitrary 100 percent, whereas the data of Wang's Fig. 5 show that even with a combination of peptides IIF and IIID, the resulting synthetic peptide antigen assay did not perform as well as the then industry standard SOD-C100 fusion protein. That latter material is also noted at column 15, line 29, in footnote 18 that cites the Chiron EPO patent application (EPO 0318218AT, 1989). Thus, all of the results of Wang pertinent here are

related to results obtained using a peptide that performed as antigen more poorly than did the C100 recombinant non-structural protein.

Turning back to Wang's Table 7 and Example 14, it is seen that the best results obtained were only 98.6 percent as good as that of peptide IIID, and were thus worse than using SOD-C100. Those results were obtained with peptide VIIIE that included residues 2-62 of the capsid protein that correspond to residues 1-62 of Fig. 1 herein. Peptides VIIIA-VIIID (positions 41-, 31-, 21- and 11-²~~120~~ of the capsid protein), also relied-on in the Action, provided only 27.5, 54.8, 70.2 and 84.1 percents, respectively, of the result obtained with peptide IIID, and would thus be still poorer than those with SOD-C100. Peptide IXC that begins at residue ²⁵73 and continues through the C-terminal Gly also showed a similar binding value of 57.1 percent, indicating no benefit for antibody binding in the synthetic peptide by the presence of residues 65-73 of the mature protein.

The Examiner's attention is now invited to pages 53 through 76 of the present specification and to Tables 2-7 therein. Comparative data are provided there between various assays that utilized several different assay techniques, of which three are of import here.

The first of those techniques utilized the alanine transferase (ALT) enzyme detection method discussed and cited at page 70, lines 1-2; and used in some of the Wang teachings, e.g. Example 15. The second utilized the C100 antigen of a commercial kit that corresponds to the SOD-C100 of the Chiron EPO patent application noted in Wang and referred to there as anti-HCV. The third used recombinant antigens of the present claims designated CAP-N and CAP-B.

21-4.

The CAP-N antigen contains amino acid residues 1-74 of Fig. 1 herein or residues 1-74 of the structural NANBV protein now referred to as the capsid or core. Construction of that recombinant molecule is discussed at pages 53 through 55. The references there to use of plasmid pGEX-3X-690:694 that relate back to pages 48 and 49, Table 1 indicate that the plasmid contained DNA that encoded amino acid residues 1 through base 74 (224 bases/3) of the NANBV structural protein. The CAP-B recombinant antigen is similarly discussed at page 64. Both antigens are also discussed in the footnotes to Table 7 at page 75. Preparation of a recombinant 1-120 antigen is discussed at pages 60-62.

Turning back to the data between pages 69 and 76 of the present application, it is seen that use of the recombinant CAP-N antigen to bind to NANBV antibodies out-performed the commercial assay kit based on the C100 antigen. For example, Table 2 shows that an assay of the present invention detected antibodies four weeks earlier than did the C100 antigen. Table 3 shows that the C100 antigen never detected antibodies over a 23-week period, whereas a claimed assay detected antibodies at 14 weeks. Table 4 shows that anti-CAP-N antibodies were detected at 4 weeks post infection, whereas the industry standard and the standard against which Wang's peptides were ultimately tested found those antibodies only at 18 weeks. The results of Table 5 are similar, but show a difference only at 2 weeks with the next entry at 40 weeks showing a similar result. The data in Table 6 again show failures by the industry standard where an assay of the present invention showed infection.

The data in Table 7 show on the whole that the CAP-N recombinant antigen and the CAP-B recombinant antigen were very similar in detecting anti-HCV antibodies, and that the

results with the recombinant CAP-B antigen also therefore surpassed those with the C100 antigen. Those data also show both recombinants to surpass the results obtained using either the CAP-A recombinant (positions 1-20) or the CAP-C recombinant (positions 41-60).

Those data further show that use of the shorter position 21-40 sequence of the present claims can offer some advantage in sensitivity over the position 1-74 CAP-N sequence for some human sera. See, for example, patients 191-2 and 216-1. This finding is certainly unexpected.

Tying the above strands of data together between the Wang disclosures and those of the present inventors, it is seen that Wang in Table 7 and Example 14 at best obtained immunoreactivities poorer than those obtained using the C100 antigen. On the other hand, the present inventors, using their recombinant antigens obtained results that far surpassed those obtained using the C100 antigen.

It is submitted that if a claimed recombinant were the same as, obvious from or equivalent to that of Wang, a similar result should have been obtained between Wang and the present inventors. That similar results were not obtained, and that unexpectedly enhanced results were obtained by the present inventors bespeaks of the unobviousness of a claimed assay that utilizes a recited recombinant. Those unexpected and unobvious results should not go unrewarded and this rejection should be withdrawn.

*not limited
to research
from CAP-C*

It should also be noted that Wang's Examples 15-18 illustrate that sensitivities similar to those obtained here with assays based upon a recombinant antigen were not obtained by Wang until mixtures of synthetic peptides from both structural and non-structural (NS) proteins were used. For example, Example 15

of Wang states that "Format C incorporating peptides (IIH, V and VIIIE) from both the HCV structural (core) and non-structural regions was the most sensitive". (Column 43, lines 26-29.) Thus, again the unexpected result obtained with a present core-only recombinant antigen assay as compared to Wang's mixed synthetic peptide assay indicates that a claimed assay has unexpected results, and that this rejection should be withdrawn.

Thus, the before-discussed unexpected differences in immunoreactivity, must be due to Wang's use of a chemically synthesized peptide as compared to the present inventors' use of a recombinant protein portion.

C. Rejection Under 35 U.S.C. §103

Claims 37-46 were rejected as allegedly obvious over Wang in view of Kuo et al. Kuo et al. (hereinafter Kuo) teaches the production of the recombinant SOD-C100 antigen of the Chiron EPO application and commercial kit used comparatively by the inventors here. The Action asserts that it would have been obvious to prepare a Wang peptide using the Kuo techniques "to gain the advantages of producing peptides by recombinant means, e.g. to obtain a stable, plentiful supply of peptides that are free of contamination (of other HCV peptides)." This rejection is respectfully traversed.

It is first submitted that inasmuch as independent claim 35 has been shown to be new and non-obvious, as discussed above, claims 37-46 that depend from claim 35 can also not be obvious. Thus, this rejection should be withdrawn.

Second, it is submitted that the best way to make a peptide free of other HCV antigens, host cell antigens as well as other possible antigens is to do what Wang did, build it by chemical syntheses. Such chemical syntheses using only organic solvents and t-Boc-blocked amino acids assure an absence of

related antigens. Thus, the conclusion reached for using a Kuo technique is incorrect and this rejection should be withdrawn.

Third, Kuo used yeast to make his recombinant. Yeast typically exclude inserted plasmids after several generations and are not a "stable" source of a recombinant. Again, this rejection should be withdrawn.

Fourth, it is far more difficult to obtain a useful recombinant than it is to obtain a chemically produced, synthetic peptide as did Wang. The work-up of cell lysates required to obtain the desired recombinant protein or fusion protein is typically far more arduous than is the work-up from peptide synthesis, where programmed machines do most of the work and an HPLC separation of the cleaved, deblocked peptide can provide the useful material. It is further understood that expression in yeast cells as done by Kuo is usually not as efficient as expression in E. coli, thereby making purification still more difficult. The rejection should be withdrawn.

In addition, although it is asserted that materials of claims 4, 43, 44 and 46 are not explicitly taught in Wang or Kuo, they are well known and that their substitution for the materials of Wang or Kuo would be obvious. As the Court held in Smithkline Diagnostics, Inc. v. Helma Laboratories Corp., 8 USPQ 2d 1468, 1475 (Fed.Cir. 1988), "one cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention". [Citation omitted.] Here, no references have even been provided for this point and still a picking and choosing has occurred. Thus, again this rejection should be withdrawn.

III. THE PRINCE DECLARATION

Also enclosed herewith is a true copy of a Declaration of Dr. Alfred M. Prince that was submitted in co-pending

application Serial No. 07/573,643, that is also before the Examiner. Dr. Prince is the leader of the New York Blood Center research group involved with this application and a named inventor herein. As noted by the Wang research group in the first line of enclosed Document BA that is discussed hereinafter, it was Dr. Prince who named NANBV as hepatitis C virus.

of Prince's Declaration
Dr. Prince's Declaration provides data that illustrate efficacy of a claimed assay based on the whole recombinant capsid protein from amino acid residue position 1 through 120 of Fig. 1. Table 1 of Dr. Prince's Declaration provides exemplary data similar to the data of pages 69-76 of the present specification for assays using the above recombinant protein that contains the capsid 1-120 sequence. Those data show optical density values for the C100 and recombinant antibody binding studies for nine transfusion patients whose sera tested negative in a C100-based assay and which sera were found positive using the recombinant 1-120 region antigen. Those data, like the data for the CAP-N recombinant illustrate that that claimed recombinant is also more immunologically sensitive than the C100-based assay and detected antibodies after a period of months in which the latter assay continued to show negative results as to infection.

Thus, the unexpected results obtained using the CAP-N and CAP-B recombinants are also observed using the 1-120 recombinant. All three were more sensitive than the C100-based assay, which itself was more sensitive than that shown using peptide VIIIE as antigen as is disclosed in Wang's Table 7 and Example 14.

Dr. Prince's Declaration continues with a discussion of his studies of assay kits provided by Dr. Wang's associates at United Biochemical, Inc. (UBI), the assignee of the Wang patent. Three types of kits were provided that were labeled "ST", "NS"

and "HCV". Although the specific antigens in each were not identified, Dr. Prince was informed by Dr. Barbra Hosein of UBI that the kit labeled "ST" contained synthetic peptide from a structural protein, that labeled "NS" contained non-structural protein synthetic peptide, and that labeled "HCV" contained synthetic peptides from structural and non-structural proteins. He presumed that those three kits contained the antigens of the assays described in the Hosein et al. article that is enclosed as Document BA.

Inasmuch as Dr. Prince's Declaration and the discussion in IV, below, correlate the data between the Hosein et al. paper and data of the Wang patent for Formats A and C, and the UBI kits Dr. Prince's group used are presumably those of the Hosein et al. paper, above, identification of the antigens in the UBI kits provided to Dr. Prince is possible. The kit labeled "ST" contained peptide VIIIE, that labeled "NS" contained peptides IIH and V, and that labeled "HCV" contained all three.

The kit labeled "ST" and containing peptide VIIIE was used for the comparative studies of Table 2 of Dr. Prince's Declaration, whereas the kit labeled "HCV" containing all three peptides was used for studies in the enclosed Sugitani et al. paper that is referred to herein as Document BB and is discussed hereinafter.

The data in Table 2 of Dr. Prince's Declaration show pertinent data for a chimpanzee designated Chimpanzee No. 10 inoculated with virus in 1977 and from which blood samples were taken and stored over a period of several years. The data of Table 2 show that for that chimp, the claimed assay based upon the recombinant capsid 1-120 sequence was able to detect infection whereas the UBI-ST kit based on the Wang peptide VIIIE

as antigen showed no evidence of infection during the acute phase of the infection nor during the chronic phase.

Thus, again, the unexpected advantage of using an assay based on a recombinant antigen of the invention over a similar chemically produced antigen was shown.

IV. FURTHER ART

Five papers of possible interest here, at least four of which were published after the filings of both Wang and the present application, have come to counsel's attention and are noted here to complete the record and underscore that which has already been discussed. The first paper published is by Wang and her co-workers [Hosein et al., Proc. Natl. Acad. Sci. USA, 88:3647-3651 (May 1991)]. The second is by two of the present inventors and their co-workers [Sugitani et al., Lancet, 339:1018-1019 (April 1992)]. The third, by inventors herein [Nasoff et al., Proc. Natl. Acad. Sci. USA, 88:5462-66 (1991)] was published prior to the Wang paper. The fourth paper is Okamoto et al., Japan. J. Exp. Med., 60:222-233 (1990), whereas the fifth is Okamoto et al., Hepatology, 15:180-186 (1992).

Copies of the above papers are enclosed herewith as documents BA, BB, BC, BD and BE, respectively. They are also noted on enclosed Form PTO-1149.

The first paper (BA) discusses assays run using chemically synthesized peptides. An unidentified capsid (core) peptide "selected from a region covered by amino acids 1-120" was used as the single antigen in EIA I, peptides from two non-structural proteins were used in EIA II and all three peptides were used in EIA III. These three formats are thus similar to Formats A, B and C of the Wang patent.

Although there is not an exact identity of data (presumed to be due to the typographical errors because of the

complete identity of the remaining data), it is believed that the data of Table 1 of this paper for donor 1 are the same as those of Table 8 of the Wang patent for panel 1. Similarly, the results of the second paragraph on the left side of page 3649 for Japanese dialysis patients can be obtained by ready calculation from the data of the Wang patent Table 9. That being the case, the peptides of EIA II correspond to those of Format A of the Wang patent, whereas the EIA III peptides are those of Format C of the patent that used peptides IIH, V and VIIIE. Inasmuch as EIA III is said in the paper to contain all three peptides of EIA I and EIA II, the peptide of EIA I must have been peptide VIIIE of the patent.

This paper discusses the added sensitivity of anti-HCV antibody detection when a capsid synthetic peptide is added to peptides from non-structural proteins, including earlier detection of seroconversion as compared to the C-100 antigen-based assays. Missing, however, are data for the capsid synthetic peptide alone; i.e., peptide VIIIE.

The second paper (BB) compares various assays that include a Wang group kit (UBI-HCV, reference 5) an assay of the present invention (Capsid) and C100 Kit used for comparison herein (C100-3). The data of the table show that an assay of the present invention based on a recombinant capsid corresponding to residues 1-120 was equally sensitive to the UBI-HCV kit containing three peptides and a second generation kit from Abbott (Abbott-II) that contains two non-structural antigens and a capsid antigen. All three identified 13/19 or 68 percent of the PCR-positive sera.

Thus, another unexpected result is found here. An assay of the claims based on a single recombinant whole protein (Fig. 1., residues 1-120) was as sensitive as an assay based on a

mixture of three chemically synthesized peptides from three different proteins.

Enclosed paper three (BC) describes the CAP-N antigen used in the present application. Although the nomenclature is different, it is apparent that the capsid antigen designated CAP-A of BB is the CAP-N antigen of the present application.

Document BD is an apparent follow-up to the Okamoto et al. paper of record herein that is cited twice in the paragraph bridging pages 1 and 2 of the present application. This paper deals with the use of a 36-mer synthetic peptide that contains residues 39-74 of the HCV capsid as an antigen in an assay for anti-HCV antibodies.

The first page of the article indicates that it was received for publication on June 13, 1993. A computer-assisted search in the MEDLINE data base of DIALOG Information Services, Inc., indicates that Document BD was published in August of 1990. The mailing and receipt dates of this article are unknown, but are being sought from counsel's Japanese associates and will be provided to the Examiner on receipt.

As is seen from the Summary, the anti-synthetic peptide assay (anti-CP9) and the commercial anti-HCV assay overlapped with positive results in 54 percent of 324 cases of acute or chronic NANB liver disease, with 18 percent of the sera being positive only in the anti-CP9 assay and another 15 percent of the sera being positive in the anti-HCV assay and negative in the anti-CP9 assay, leaving another 13 percent undetected in either assay.

Document BE published in 1992 is an apparent follow-up to Document BD. Here, another synthetic peptide was used in the assays. That peptide was designated CP10, and includes 19 residues covering amino acid residue positions 5-23 of Fig. 1.

It is noted that this paper used the two peptides separately and summed the results obtained from separate assays rather than linking the peptides or using a mixture of both in the assays.

V. SUMMARY

The specification has been amended to correct an obvious error in typing and the claims have been amended to recite use of only recombinant antigens that include HCV residues 21-40. Each of the bases for rejection has been dealt with and overcome or otherwise made moot. A copy of a Declaration of one of the inventors is enclosed that provides further data for a claimed recombinant as well as information regarding data by the inventors and Dr. Wang and her research group that were published subsequent to the filing dates of this application and the Wang patent. Copies of those papers are enclosed.

It is therefore believed that the application is in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

By Edward P. Gamson
Edward P. Gamson, Reg. No. 29,381

Enclosures

Petition and fee
Prince Declaration and enclosure
Further art (BA-BE)
Form PTO-1449

CERTIFICATE OF MAILING

I hereby certify that this Amendment Under 37 C.F.R. §1.115, together with the stated enclosures, is being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on January 28, 1993.

Edward P. Gamson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#16
XP
2-12-93

Applicant:	Zebedee et al.)	
Serial No.:	07/573,643)	Attorney Docket
)	PHA 0025P
Filed:	August 27, 1990)	
)	Group Art Unit: 1802
For:	NON-A, NON-B, HEPATITIS VIRUS)	
	ANTIGEN, DIAGNOSTIC METHODS AND)	
	VACCINES)	
Examiner:	D. Wortman)	

DECLARATION OF ALFRED M. PRINCE, M.D.

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

ALFRED M. PRINCE, M.D., Declares

1. That he is the Alfred M. Prince who is a named co-inventor of the subject matter of the above-identified patent application;

2. That he is employed by the Lindsley F. Kimball Research Institute, a Division of The New York Blood Center (NYBC), an assignee of the above-identified patent application;

3. That a true and accurate copy of his Curriculum Vitae entitled "Biographical Sketch" is attached hereto that lists, inter alia, his educational background, work history, awards and the almost three hundred published papers and book chapters of which he is a sole or joint author, including approximately thirty-seven publications relating to hepatitis C virus;

4. That he has read and is familiar with the outstanding Office Action on the above-identified patent application, the art relied-on in that Action, and the Response filed herewith;

5. That he is the head of the Laboratory of Virology at the NYBC and is the leader of the NYBC research group that carried out the work at that institution related to this patent application;

6. That he and those under his direction and control have continued work on the invention defined by the presently amended claims;

7. That as part of that continued work, a number of serum samples were obtained from transfused human patients that were screened for anti-HCV antibodies using a commercially available assay that contained the recombinant C100 antigen and were found to not contain such antibodies;

8. That those sera were also screened in an assay of the amended claims using a recombinant antigen containing residues 1-120 of application Fig. 1 as the only antigen, and about 5 to about 10 percent of those sera were found to contain antibodies that bound to the recombinant antigen;

9. That not only were those previously negative anti-HCV antibody-containing sera found to be positive for the presence of those antibodies in a presently claimed assay, but in three exemplary instances, an assay of the present invention was positive for the presence of those antibodies over an infection period of one to three months during which time the C100-based assay showed the sera to be negative;

10. That the optical density values obtained for the sera from nine C100 assay-negative patients discussed in Paragraphs 8 and 9, above, are shown below in Table 1, in which the numbers at the left show the patient number, the "week" is the week post transfusion, "C-100" is the observed optical

density using that assay with the "-" sign thereafter indicating a negative assay for anti-HCV antibodies, and "CAP" being the optical density values obtained using the recombinant 1-120 residue capsid antigen with the "+" sign indicating a positive response in the assay;

Table 1

Transfusion Patient
Sera Positive for Antibody to CAPSID
1-120 and Negative for Antibody to C-100

<u>Patient #</u>	<u>WEEK</u>	<u>C-100</u>	<u>CAP</u>
9	4	0.08-	0.47+
18	7	0.18-	1.93+
18	10	0.2-	1.88+
18	17	0.12-	1.91+
92	21	0.12-	1.33+
92	22	0.03-	1.59+
92	24	0.18-	1.33+
117	10	0.09-	0.48+
169	14	0.12-	1.1+
169	16	0.36-	1.1+
169	19	0.14-	1.88+
169	21	0.11-	1.69+
169	23	0.17-	1.74+
201	8	0.12-	0.6+
213	13	0.24-	0.81+
257	10	0.25-	0.88+
299	8	0.09-	0.46+

*CAP for 1-120 is?
O.D. values based
on unit?*

11. That in a further aspect of his research group's work with the present invention, he was provided with three solid phase assay kits by Dr. Barbra Hosein, one of Dr. Wang's associates at United Biochemical, Inc. (UBI), the kits being labeled "ST", "NS" and "HCV";

12. That he was not informed of the specific antigen utilized in each kit, but he was informed that the kit labeled "ST" contained synthetic peptide from a structural protein, that labeled "NS" contained synthetic peptide from non-structural protein, and that labeled "HCV" contained synthetic peptide from both structural and non-structural proteins;

13. That he presumed that the peptide antigens of those kits were those described in Hosein et al., Proc. Natl. Acad. Sci. USA, 88:3647-3651 (1991) that is enclosed with the accompanying Response as Document BA;

14. That the Hosein et al. article (Document BA) does not specify the synthetic peptide antigens used by sequence position, but the substantial identity of the data in Table 1 of Document BA with those of the Wang patent Table 8, panel 1, the identity between the results discussed on the left side of page 3649 of Document BA and the data of Table 9 of the Wang patent, and his presumption of Paragraph 13 permit him to come to a belief as to the identities of the specific synthetic peptide antigens used in Document BA and in each kit he received;

15. That it is his belief that the synthetic peptide antigens used in the kits he received, the Hosein et al. paper (Document BA) and the Wang patent are as shown below:

<u>UBI Kit</u>	<u>Hosein et al. (Doc. BA)</u>	<u>Wang Patent Format</u>	<u>Wang Patent Peptide</u>
NS	EIA II	A	IIH & V
HCV	EIA III	C	IIH, V & VIIIE
ST	EIA I	---	VIIIE

16. That enclosed with the Response as Documents BB and BC are true copies of two papers published after the filing date of the above-identified application that are authored by him and his co-inventors and co-workers;

17. That with one exception, the data and disclosures of those two papers were believed at the times of their submission, publication and are now believed to be true and correct;

18. That the one exception in Paragraph 17, is that footnote 6 (to Document BC) was cited in error in that the results reported for the "Capsid" of the table of Document BB

were obtained using a recombinant protein containing amino acid residues 1-120 of application Fig. 1 as in Table 1, above in Paragraph 10, rather than a shorter recombinant of Document BC;

19. That the results shown in the table of Document BB illustrate that use of the single recombinant protein containing residues 1-120 of Fig. 1 of this patent application were the same as those obtained using the UBI-HCV (presumed Wang synthetic peptides IIH, V and VIIIE) assay and were better than those obtained using the C100 antigen-based assay;

20. That in still further work related to the present invention, results obtained using an assay based on the claimed recombinant 1-120 residue sequence antigen were compared with results obtained using the UBI kit labeled "ST" (the kit believed to use Wang patent VIIIE as antigen), using sera obtained from chimpanzees infected with HCV and from which blood samples were taken and stored over a period of years;

21. That the results for those sera were comparable with the exception of the sera from a chimpanzee designated Chimpanzee No. 10;

22. That chimpanzee No. 10 was inoculated with HCV in November of 1977, with blood samples being taken throughout 1978 and thereafter; the animal being rechallenged with HCV during the sample-taking time period;

23. That pertinent data related to the serum samples from Chimpanzee No. 10 are provided below in Table 2, whose entries have the following meanings: Date = date data were taken; Week = week prior or subsequent to inoculation with HCV; HIST = histological evaluation of liver tissue biopsy, in which NORM means a normal appearance, NSRH means non-specific reactive hepatitis, AH means acute hepatitis, and CPH means chronic

persistent hepatitis; CAP the optical density (O.D.) reading using an assay based on the recombinant 1-120 sequence of Fig. 1 as antigen, with an O.D. of 0.35 or greater indicating a positive result, and N indicating a negative result; and UBI-ST = O.D. values obtained using a provided UBI kit designated "ST", with the dash after the number indicating a negative finding.

Table 2Data for Chimpanzee No. 10

<u>Date</u>	<u>Week</u>	<u>HIS</u>	<u>CAP</u>	<u>UBI-ST</u>
11-08-77	-2	NORM	N	0.01-
12-27-77	6	NORM	N	0.05-
02-07-78	12	NSRH	N	0.04-
03-21-78	18	AH	0.52	0.01-
05-02-78	24	AH	0.49	0.01-
06-13-78	30	AH	0.48	0.00-
07-25-78	36	CPH	N	0.01-
11-09-78	51	CPH	---	0.02-
11-23-78	53	CPH	0.47	---
12-04-78	55	CPH	---	---

for info
CAP &
Russian
2/20
1-120

24. That the data of the studies shown and particularly Table 2 show that a claimed assay utilizing a recited recombinant as the sole antigen performed better than did an assay based on a single synthetic peptide having most of the same sequence, in that an assay of the present claims detected HCV infection in both the acute and chronic forms, whereas the assay based on the similar synthetic peptide detected neither type of infection;

25. That he further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may

Serial No. 07/573,643

-7-

jeopardize the validity of any patent issuing on this application.

Date

1-27-93

Alfred M. Prince, M.D.

Enclosure

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington D.C. 20231,

on January 28, 1993

DATE OF DEPOSIT

EDWARD P. GAWSON

TYPED OR PRINTED NAME OF PERSON MAILING

Edward P. Gawson

SIGNATURE

January 28, 1993

DATE OF SIGNATURE

[illegible]



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
616369	11-21-90	Zebedee	PHA0026

EXAMINER	
Wortman	
ART UNIT	PAPER NUMBER
1802	18

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Examiner Wortman (3) T. Helting
(2) E. Gamson (4)

Date of Interview 2-23-93

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No. If yes, brief description:

Agreement ☐ was reached with respect to some or all of the claims in question. ☒ was not reached.

Claims discussed:

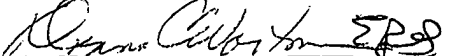
Identification of prior art discussed: Wang US Patent 5106726

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Comparison between Wang's ^{synthetic} peptides and instant recombinant peptides of HCV core region was discussed. Supplemental response will be submitted.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview.
☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.


Examiner's Signature



182/24/43
071

waitman

#19
2-26-92

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 07/616,369) Attorney Docket
Filed: November 21, 1990) PHA-0026P
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: D. Wortman)
Group Art Unit: 1802

Supplemental Response

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

RECEIVED
93 FEB 25 AM 7:48
GROUP 180

Sir:

This is to supplement the Response filed on January 28, 1994 for the subject application.

A. Document BD

Document BD supplied with the prior Response bore a publication date of August 1990 on its face. That Response noted that the specifics of the publication were being sought from counsel's associates in Japan, and that those specifics would be supplied on receipt.

It is first noted that the third full paragraph on page 15 of the prior Response, which discussed Document BD, states that the article bears a statement that it was received for publication on "June 13, 1993". That date was an inadvertent error and should have been "June 13, 1990". Counsel regrets any inconvenience that error may have caused.

As to Document BD, Okamoto et al., Jpn. J. Exp. Med., 60(4):223-233 (1990), enclosed herewith as Exhibit I is a true copy of a fax received by counsel from Mr. Nobuo Ogawa of Nakamura & Partners, counsel's Japanese associate.


As will be seen from Exhibit I, there is a one-month disagreement between the date of mailing provided by the publisher and receipt date by libraries in the Tokyo area. Nevertheless, the earliest date, the receipt date, appears to be October 31, 1990, a date about two months after the filing date of application Serial No. 07/573,643, the parent of the present application. It is thus submitted that Document BD is not prior art here.

B. Further Art

Further art and an Action citing that art from co-assigned Application Serial No. 07/819,360 that also deals with HCV have been received. Non-redundant copies of that art (labeled Documents CA-CK) and the Action are included with a copy of a paper similar to this paper filed on even date with this paper for for parental application 07/573,643. That art is listed on enclosed Form PTO-1449.

No further fee or petition is believed necessary. However, should any further fee be needed, please charge our Deposit Account No. 04-1644, and deem this paper the required Petition.

Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381

Enclosures

Exhibit I
Copy of Action in Ser. No. 07/819,360
Form PTO-1449

CERTIFICATE OF MAILING

I hereby certify that this Amendment Under 37 C.F.R. §1.115, together with the stated enclosures, is being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on February 12, 1993.



EXHIBIT I

NAKAMURA & PARTNERS
PATENT TRADEMARK & LEGAL AFFAIRS

Formerly

NAKAMATSU

International Patent & Law Office

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 CABLE: NAKAPATENT

K. NAKAMATSU
 (1895-1973)

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M. MIRAI	A. NAKAZAWA
M. IMAMURA	K. OKA
T. ISHIKAWA	T. ORITA
H. ITAKI	Y. SHIMAZOE
E. JITSUKAWA	I. TADANO
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 A. NAKODA
 T. NISHIURA
 A. OSHIMA
 K. TSUBOI

COUNSELLOR
 K. NISHIMOTO

February 4, 1993
 VIA FACSIMILE

Dressler, Goldsmith, Shore,
 Sutker & Milnamow, Ltd.
 Two Prudential Plaza
 Suite 4700
 Chicago, Illinois 60601
 U. S. A.

Attention: Mr. Edward P. Gamson

Re: Okamoto et al.
 Japanese Journal of Experimental Medicine
 60(4):223-233(1990)
 Your Ref.: NYBC 0025P and 0026P
 Our File: IFX-0011/MI/SEM

Dear Mr. Gamson:

Thank you for your letter of January 23, 1993 with respect to the above-identified journal published in Japan.

In accordance with your instructions, we have contacted KINOKUNIYA COMPANY LTD., the publisher of the subject journal. We talked to Mr. Masayuki FUNAMOTO of publication department about the mailing date of the subject journal, Vol. 60, No. 4, August 1990 issue, and learned that this journal was mailed out on November 28, 1990 according to the publisher's record. We also learned that this journal was actually printed and mailed out by subcontract printing company, CHUOH INSATSU JIMUKI, and that the publisher's record as to the mailing date was prepared based on the report from the subcontractor. We accordingly contacted the subcontractor and confirmed from a conversation with Mr. Chikara TAKIGUCHI that the

mailing date according to the subcontractor's record is exactly the same day, November 28, 1990. All of these conversation were made over the phone with Mrs. Setsuko MAYAMA, a patent attorney of our firm.

We, however, learned that the National Diet Library in Tokyo, one of the biggest comprehensive libraries in Japan, received the subject journal on October 31, 1990, one month before (not after!) the publisher's mailing date. The subject journal was sent to this library by mail and receiving date was indicated as a datemark on the front page of the journal. According to a library clerk of this library, the subject journal was probably available to the public a few days after the date of receiving, however, such date could not be identified since it is not a matter of record.

We also contacted departmental libraries of the University of Tokyo, i.e., the Medical Library and the Library of Faculty of Agriculture, and learned that the subject journals were independently sent by mail to these libraries on October 31 and November 1st, 1990, respectively. We were advised by a library clerk of the Medical Library that most journals and books are available to the university students on the very day or one day after the receiving date.

From the foregoing, we presume that the subject journal was received by libraries in Tokyo on October 31, 1990, at the earliest, and was available to the public at least by the end of the first week of November 1990, and that it would be most reasonable to consider that the subcontractor inadvertently recorded the incorrect mailing date and reported the incorrect date to the publisher. We again inquired the publisher and the subcontract printing company only to find that their records positively indicate the identical mailing date of November 28, 1990, approximately one month after the actual receiving date and that no other record was made by the subcontractor as to the mailing date that can be evidence to verify the actual mailing date.

We hope that you find the foregoing information sufficient for

your business purpose. If you have any questions or need further information, please do not hesitate to contact us again.

We will provide our debit note for services related to the above with the confirmation copy of this facsimile letter.

Very truly yours,

N. Ogawa

Nobuo OGAWA

MI/SEM/-



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/819,360 01/10/92 KE

N 19 E

L NYBC-001

DRESSLER, GOLDSMITH, SHORE, SUTKER &
MILNAMOW, LTD.
TWO PRUDENTIAL PLAZA-SUITE 4700
180 NORTH STETSON AVENUE
CHICAGO, IL 60601

DURRUE, C

1813

9

DATE MAILED: 01/13/93

☒ This application has been examined ☒ Responsive to communication filed on 10/28/12 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input checked="" type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-25 are pending in the application.
Of the above, claims 10, 11, 9, 5-25 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-9 + 12-14 are rejected.
5. ☐ Claims _____ are objected to:
6. ☒ Claims 1-25 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____ Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Serial Number: 07/819,360

-2-

Art Unit: 1813

15. This Application has previously been restricted under 35 U.S.C. § 121 (paper No. 7), and Applicants have responded in paper No. 8 to that requirement. Upon receiving the transferred case into Art Unit 1813, Examiner Dubrule determined that the prior requirement might be altered for clarity. The new Groups then are outlined below:

16. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-9 and 12-14, drawn to peptides, immunogens and methods of immunizing, classified in Class 530, subclass 350 and Class 424, subclass 89.

II. Claims 10 and 11, drawn to antibodies, classified in Class 530, subclass 387.1.

III. Claims 15-21, drawn to assay methods for antibodies and kits, classified in Class 435, subclass 5.

IV. Claims 22-25, drawn to DNA molecules and assays using them, classified in Class 536, subclass 27 and Class 435 subclass 6.

17. The inventions are distinct, each from the other because of the following reasons:

18. The peptides of Group I could be used to generate the antibodies of Group II, or they could be used in antibody assay methods, as in Group III.

19. The antibodies of Group III could be used for diagnostic purposes (i.e., antigen capture), therapeutic purposes, or in purification schemes.

20. Group IV is distinct from the other Groups because DNA molecules are chemically distinct from protein molecules, and are useful for other purposes than encoding proteins, such as the assay of Group IV.

21. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

22. During a telephone conversation with Edward Gamson on 1/7/93 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-9 and 12-14. Affirmation of this election must be made by applicant in responding to this Office action. Claims 10, 11 and 15-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Serial Number: 07/819,360

-3-

Art Unit: 1813

23. The disclosure is objected to because of the following informalities: Page 73 of the specification reports at line 28 that 9 liters of RNase-free water were used to resuspend RNAs. The Examiner believes that this may be a typographical error. Page 80 of the specification refers to a Genbank Accession number, but fails to provide this number. The specification at page 81, line 21 refers to "the four major prototypes HCV-1, HCV-J and HCV-BK", which list includes only three major prototypes. Appropriate correction is required.

24. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure, and failing to adequately describe the invention.

26. The specification fails to teach Korean isolates of HCV. While the specification does characterize the Chinese isolates as belonging to the same group as Korean isolates, it is unclear how this conclusion was reached. The specification provides no sequence or homology data for Korean isolates, therefore claims directed to Korean isolates or sequences are not adequately described, in an enabling fashion.

27. The specification fails to teach "non-HCV-PRC-Korean unique" peptides or proteins, as recited in claim 6. As mentioned below, it is unclear what is meant by this phraseology, but for the purposes of this rejection the Examiner interprets it to mean "all peptides which are unique, but which are not derived from the PRC or Korean isolates". Clearly, the specification fails to teach such unique sequences. If Applicants intent was to claim non-unique portions of the PRC-Korean isolate, alternative language should be employed.

28. Claims 6, 7, 11 and 14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Serial Number: 07/819,360

-4-

Art Unit: 1813

29. Claims 6-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

30. As mentioned above, it is unclear what is meant by the term "a non-HCV-PRC-Korean unique". Perhaps affirmative language would be clearer.

31. Claims 12-14 are indefinite because it is unclear what is meant by the term "immunologically effective". Applicants do describe "effective amount" in the specification as that amount which can evoke an immune response (see page 48), but it is unclear if this defines the "immunologically effective" amount.

32. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

33. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Art Unit: 1813

34. In order to clarify the record, the Examiner wishes to point out how the peptide claims are being interpreted. Claims to peptides, or which contain peptides within the claims are interpreted as follows:

A peptide having the amino acid sequence. - the peptide is the defined sequence, and does not include any other amino acids, i.e. NH_2 -(defined peptide)- COOH . This is equivalent to the judicially accepted term "consisting of".

A peptide which contains a peptide. - The peptide may include other amino acid residues, i.e. NH_2 -X-(defined peptide)-Y- COOH , where X and Y can be peptide or protein, or can be optionally not included. This is equivalent to the judicially accepted term "comprising".

35. Claim 1 is rejected under 35 U.S.C. § 103 as being unpatentable over Highfield et al, GB 2,239,245 in view of Lipka et al, 1990 and Washitani et al, 1991.

36. Highfield et al describe a novel isolate of HCV and its predicted amino acid sequence. One of the sequences (ID No. 3) contains the sequence of ID NO. 64 of the instant application (at residues 147-152). While the claim language of claim 1 excludes the intact protein represented by ID No. 3 of Highfield et al, the peptide is obvious from their disclosure. This is because the sequence of HCV is well known to vary greatly among isolates (see for example Ogata et al, 1991, Weiner et al, 1991, Choo et al, 1991 and Hijikata et al, 1991), therefore any portion of the sequence which is unique to an isolate or group of isolates would be useful to develop typing reagents, or to detect antibodies specific for that isolate. Both Lipka et al, 1990 and Washitani et al, 1991 teach the utility of such typing reagent to identify subtypes of viruses.

37. Claims 1-7 and 12-14 are rejected under 35 U.S.C. § 103 as being unpatentable over Highfield et al, Ogata et al, 1991, Weiner et al, 1991, Choo et al, 1991 and Hijikata et al, 1991, in view of Lipka et al and Washitani et al.

38. In each of the above cited primary references, standard cloning techniques were used to isolate and sequence various isolates and regions of HCV. Highfield et al teach the use of fusion proteins of HCV, as well as the use of antigenic regions to generate antibodies. A fair reading of the references teaches the heterogeneity of isolate sequences. In view of these references, the skilled artisan would have expected that novel isolates of HCV would have possessed unique regions.

Serial Number: 07/819,360

-6-

Art Unit: 1813

39. The Examiner admits that the sequences represented in claims 1-6, with the exception of ID No. 64, fail to appear in the prior art made of record herein. Additionally, the skilled artisan would have been unable to predict what those sequences may have been based upon the prior art. However, it appears well known that the sequences of various isolates of HCV vary substantially (see above). Therefore, the fact that Applicants were able to isolate RNAs of HCV isolates which diverge from known isolates cannot be characterized as unexpected.

40. The motivation for identifying and producing peptides corresponding to unique regions would have been to develop typing reagents, not unlike those described by Lipka et al and Washitani et al.

41. In rejecting these claims, the Examiner is relying in no small part upon the decision the Board reached in Ex Parte Erlich, 22 USPQ 2d, 1463-1468. In this decision, the Board concluded that the specific hybridomas claimed were obvious over the prior art. Clearly, the specific cell lines claimed could not identically be reproduced by the skilled artisan, because of the complexity inherent to a composition such as a cell, but cell lines of similar function would have been producible.

42. While the specific sequences claimed instantly could not have been predicted based upon the prior art, the skilled artisan would have expected divergent sequences to exist in novel isolates.

43. Claim 8 is rejected under 35 U.S.C. § 103 as being unpatentable over Highfield et al, Ogata et al, 1991, Weiner et al, 1991, Choo et al, 1991 and Hijikata et al, 1991, in view of Lipka et al and Washitani et al as applied to claim 6 above, and further in view of Smith et al, 1988.

44. While Highfield et al employ fusion proteins in order to develop a more reliable assay, Smith et al teach that GST fusion proteins are easily purified. It would have been obvious to produce the expected peptides as fusion proteins as GST in order to facilitate downstream processing of the proteins (i.e. single step purification).

45. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

46. Papers related to this application may be submitted to Group 180 by facsimile transmission. papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Serial Number: 07/819,360

-7-

Art Unit: 1813

The CM-1 Fax Center number is (703) 308-4227

47. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Chris Dubrule whose telephone number is (703) 308-0708. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CJD

(50)

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NO. 07819,760	GROUP ART UNIT 1813	ATTACHMENT TO PAPER NUMBER 9	
NOTICE OF REFERENCES CITED				APPLICANT(S) We et al			
U.S. PATENT DOCUMENTS							
*	DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE	
A							
B							
C							
D							
E							
F							
G							
H							
I							
J							
K							
FOREIGN PATENT DOCUMENTS							
*	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG. PP. SPEC.
L							
M							
N							
O							
P							
Q							
OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)							
Chao et al, PNAS 88:2481-2485, 1991.							
A. Rinner et al, Virology 180:842-848, 1991							
B. Oyler et al, PNAS 88:3312-3316, 1991							
9C Smith et al, GENE 67:21-40, 1988							
Parker et al, J. Imm. 136(7): 2393-2397, 1986							
Parker et al, J. Imm. 142(3): 971-978, 1989							
Parker et al, J. Imm. 135(1): 247-254, 1985							
EXAMINER Chris Dubink		DATE 1/8/92					
* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)							

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NO. 07619360	GROUP/ART UNIT 1413	ATTACHMENT TO PAGE NUMBER 9		
NOTICE OF REFERENCES CITED				APPLICANT(S) K et al				
U.S. PATENT DOCUMENTS								
		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. & PP. DWG. SPEC.	
A								
B								
C								
D								
E								
F								
G								
H								
I								
J								
K								
FOREIGN PATENT DOCUMENTS								
		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. & PP. DWG. SPEC.
L		223 9245	6/24/91	GB	Hughes et al			
M		1010231	9/7/90	NO	Bumby et al			
N								
O								
P								
Q								
OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)								
R		D.K. pku et al, J. Intell. Dis. 162:353-357, 1990						
S		Nishitani et al, Int. J. Cancer 49:173-177, 1991						
T		Kato et al, PNAS 87:9524-9528, 1990						
U		Takamizawa et al, J. Virol. 65(3):1105-1113, 1991						
V		Okumoto et al, Jap. J. Exp. Med. 60(3):167-177, 1990						
W		Takahashi et al, IJAR, 18(15):4626, 1990						
X		Hama et al, Biotechnology J. 85(Suppl 2):72-76, 1990						
Y		Hattori et al, BBRC, 175(1):220-228, 1991						
EXAMINER		DATE						
Christoph		1/8/12						
* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)								

#20
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4279

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 07/616,369) Attorney Docket
Filed: November 21, 1990) PHA-0026P
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: D. Wortman)

SECOND SUPPLEMENTAL RESPONSE

Box Non-Fee Amendments (Pats)
Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

RECEIVED
APR 27 1993
GROUP 1800

Sir:

This is in further response to the Office Action dated October 5, 1993 to which a previous response was filed on January 28, 1993, a Supplemental Response was filed on February 12, 1993, and a personal interview was held with the Examiner on February 23, 1993.

RESPONSE

Reconsideration of the above-identified application is respectfully requested in view of the previously filed Response, Supplemental Response and the present, Second Supplemental Response.

The Examiner is thanked for the courtesies extended and comments made to Dr. Helting and counsel during their interview. This Response will address those comments.

Claims 35-46 are before the Examiner.

Inasmuch as there was no discussion during the interview of the previously outstanding rejection under 35 U.S.C. §112, first and second paragraphs, that was responded to in the Response mailed January 28, 1993, no discussion will be had here on those issues. Rather, the present response will deal with the alleged anticipation/obviousness issues and the previously filed Declaration of Dr. Prince.

A. The Second Prince Declaration

Enclosed herewith is a true copy of a Second Declaration of Alfred M. Prince, M.D., a named inventor herein. The original of this Declaration is being filed with the parental application, Serial No. 07/573,643. Dr. Prince's prior Declarations in both this application and the parental application were substantially identical as to the comments raised during the interview. It is therefore believed that a second, original, Declaration is not needed here. However, should the Examiner request such a Declaration, it can be provided.

Dr. Prince's enclosed, Second Declaration points out (Paragraphs 2-5) that the data of Paragraphs 6-10 of his previous Declaration were taken by ELISA. The procedures provided with the commercial kit (C-100 antigen) were used, and a protocol for the ELISA using a recombinant is enclosed therewith. Thus, the data of Dr. Prince's previous Paragraphs 6-10 compared ELISA to ELISA, and showed an ELISA based upon a claimed recombinant to

*Dr. Prince's
not re-submitted
here*

outperform the then industry standard, commercial C-100 antigen-based ELISA.

Paragraphs 6-8 of Dr. Prince's present Declaration point out that ELISA and immunoblot assays were also carried out as discussed in previously submitted Document BC using a recombinant 1-74 residue antigen, with the details for each of those assays being given in Document BC. Present Paragraph 8 points to Table 3 of Document BC in showing that an ELISA based on that recombinant 1-74 residue antigen also outperformed the industry standard C-100 antigen-based ELISA assay for two of three sera, whereas an immunoblot based on that same recombinant outperformed the C-100 antigen-based ELISA with four of five sera.

Paragraphs 9-15 of Dr. Prince's present Declaration discuss the identity of the antigen of the UBI ELISA kit he obtained denominated "ST" and the data obtained therewith, as compared to an ELISA based on a HCV recombinant 1-120 residue antigen. The results of those ELISA assays were discussed in Paragraphs 20-24 of Dr. Prince's prior Declaration. The present Declaration also discusses how those ELISA assays were done.

As is seen from Dr. Prince's present Paragraphs 9-15 and Exhibit II enclosed therewith, Dr. Wang has now identified the peptide antigen used in the "ST" ELISA as being both of peptides VIIIE and IXD of her U.S. Patent No. 5,106,726. Thus, the results discussed in the previous Prince Declaration Paragraphs 20-24 compared ELISA to ELISA with a recombinant

antigen and synthetic peptides covering the exact same region. Those results also showed a method using a recombinant antigen to be superior.

Paragraph 16 of Dr. Prince's present Declaration discussed how the ELISA's using others' kits and an ELISA based on the recombinant 1-120 residue antigen of previously submitted Document BB were carried out.

The immunoblot data of the application and the ELISA and immunoblot data of Dr. Prince's previous and present Declarations show the following:

(a) a method using immunoblots with a recombinant 1-74 residue antigen detected HCV infection earlier than did an ELISA assay based on the C-100 non-structural antigen (application Tables 2, 3, 4, 5 and 6; 2nd Declaration Par. 6-8; Document BC, Table 3, dagger data);

(b) ELISA comparisons between a recombinant antigen having the 1-74 residue sequence and C-100 showed the method using the 1-74 residue recombinant to be superior (Document BC, Table 3, asterisk data);

(c) ELISA method comparisons using the C-100 commercial antigen and the 1-120 residue recombinant showed the recombinant antigen to be superior (1st Declaration Par. 6-10; 2nd Declaration Par. 2-5);

(d) ELISA method comparisons using Dr. Wang's synthetic peptides VIIIE and IXD ("ST" kit) and a recombinant 1-120 residue of the claims as antigens showed a method using a

recombinant antigen to be superior to use of synthetic peptides covering the same region as antigen (1st Declaration Par. 20-24; 2nd Declaration Par. 9-15); and

(e) ELISA method data using a recombinant 1-120 residue antigen provided the same results as an ELISA method containing synthetic peptides from both structural and non-structural proteins (UBI-HCV) (1st Declaration Par. 16-19; 2nd Declaration Par. 16; Document BB).

Thus, the data provided show an assay method using a recited recombinant antigen to be: (a) superior to the C-100 antigen-based ELISA by ELISA and immunoblot, (b) superior to an antigen containing a combination of synthetic peptides covering the same region by ELISA, and (c) comparable to an ELISA using synthetic antigens from both structural and non-structural regions.

B. The Art-Based Rejections

Each of the art-based rejections was tied to the disclosures of the Wang et al. U.S. Patent No. 5,106,726, hereinafter referred to as "Wang", and each of those rejections was dealt with in the prior response. This response will therefore be limited to the unexpected results discussed in the application using a recombinant antigen having the sequence of positions 21-40, as recited in claim 35. ²ax

The Response mailed January 28, 1992 (the previous Response) noted that the data of the Wang disclosure compared assay results using an ELISA format with a synthetic peptide as

antigen. Those results were compared to Wang's synthetic peptide IIID, whose ELISA results were compared with an ELISA based on the C-100 antigen.

When ELISA results for peptides VIIIE and IXD were compared to those for peptide IIID (Table 7), and thus to an ELISA with C-100, the best that was observed was a result that was 98.6 percent as good as a C-100 antigen-based assay. The data of Table 7 (pages 74-76) of the present application relate to immunoblot data using antigens referred to as CAP-N, CAP-A, CAP-B and CAP-C that were recombinant antigens corresponding to positions 1-74, 1-20, 21-40 (claimed here), and 41-60 of the HCV capsid, structural protein.

The immunoblot data of Table 1 (page 5465) of Document BC (Nasoff et al.) that accompanied the January 28, 1993 response showed that the recombinant containing the sequence of residues 1-74 (there identified as CAP-A) was the only sequence from the group of residues 1-74, 69-120 (there called CAP-B) and 121-321 (there called CAP-C) that bound anti-HCV antibodies.

The data of Table 2 of Document BC augment the similar data of Table 7 herein and show that the short sequence region most effective for binding anti-HCV antibodies is that claimed herein as an antigen; i.e., positions 21-40 (there called CAP-2), with the amino-terminal region having positions 1-20 (called CAP-1) exhibiting poorer binding, and positions 41-60 being responsible for almost no antibody binding, as is also shown in Table 7 herein.

It is respectfully submitted that nothing in the Wang disclosures teaches a worker of ordinary skill to discard the N-terminal nineteen residues and the C-terminal eighty residues of the capsid protein (or the twenty C-terminal residues of Wang's peptide VIIIE) to arrive at a useful recombinant antigen containing residues 21-40. The prior Action asserted that deletion of the about 40 N-terminal residues of a Wang synthetic caused a decrease in binding titer. That assertion was made based on the data of Wang's Table 7.

The present claims recite a recombinant containing the sequence of positions 21-40. It is submitted that Wang's data of Table 7 show Wang's N-terminal nineteen residues to be of great import to her sequences in that without them, the titer goes down almost 30 percent.

The data of Wang's Fig. 11-1 must also be considered. There, three of the four samples showed the N-terminal nineteen residues to be quite important to the titer achieved. Wang also selected a peptide containing that nineteen N-terminal sequence for her further assays; i.e., peptide VIIIE.

It is thus submitted that Wang's teachings, as a whole, suggest to a skilled worker that the N-terminal nineteen residue sequence should be present. That sequence is absent from a claimed recombinant.

It is also submitted that Wang teaches that residues substantially beyond position 40 should also be present. There

are only teachings of such peptides, and no teachings to the contrary.

It must also be remembered that the data for Wang's synthetic peptides in Fig. 11-1 are all ultimately related to an ELISA based on the commercial C-100 antigen. The data of Fig. 11-1 were all inferior to those obtained using the C-100 antigen.

The present application teaches that using immunoblot assays, a recombinant antigen containing the sequence of positions 1-74 (application CAP-N; Document BC CAP-A) consistently outperformed that commercial ELISA. The data in application Table 7 and Document BC Table 2 show that an immunoblot method using a claimed recombinant provided very similar results to those using a CAP-N antigen. A slight preference may be shown in those data for a claimed method to be useful for distinguishing acute from chronic infection, and that direction is being pursued.

The data in Table 3 of Document BC show that the results observed with immunoblots using the recombinant 1-74 residue antigen versus a C-100 antigen-based ELISA are also generally found when the method using a recombinant 1-74 residue antigen is practiced in an ELISA format. There is no evidence of record that indicates those findings would also not apply to an ELISA-type assay using a claimed method.

It is again submitted that Wang alone or in combination with any other disclosure neither teaches nor suggests the


Serial No. 07/616,369

-9-

presently claimed subject matter. It is thus submitted that the claimed subject matter is patentable.

No further fee or petition is believed necessary. However, should any further fee be needed, please charge our Deposit Account No. 04-1644, and deem this paper the required Petition.

Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381

Enclosure
copy of Second Declaration of Alfred M. Prince, M.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Zabedee et al.)	Attorney Docket
Serial No.:	07/573,643)	PHA 0025P
Filed:	August 27, 1990)	Group Art Unit: 1802
For:	NON-A, NON-B, HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES)	
Examiner:	D. Wortman)	

SECOND DECLARATION OF ALFRED M. PRINCE, M.D.

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

ALFRED M. PRINCE, M.D., Declares

1. That he is the Alfred M. Prince who is a named co-inventor of the subject matter of the above-identified patent application and who submitted a Declaration mailed on January 28, 1993;

2. That the further data referred to in Paragraphs 6-10 in his previous Declaration were obtained using an ELISA format assay in which the recombinant 1-120 residue protein antigen was affixed to the walls of microtiter plates and used to assay for the presence of anti-HCV antibodies in sera of humans;

3. That enclosed Exhibit I is a true copy of the ELISA assay protocol used in his laboratory for carrying out ELISA assays using the recombinant 1-120 residue antigen and other recombinant antigens in similar assays;

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4. That the data of Paragraphs 6-10 of his previous Declaration, and particularly those of Table 1, using the C-100 antigen were also ELISA assays so that the data of Table 1 compare ELISA results to ELISA results;

5. That the data using the C-100 antigen ELISA were obtained following the procedures outlined in the manufacturer's (Ortho Diagnostics) instructions;

6. That the Nasoff et al. article (previously submitted Document BC) included data from assays using both immunoblot (Tables 1 and 2, page 5465) and ELISA (Table 3, page 5465) techniques;

7. That the data were taken for the recombinant 1-74 residue antigen (CAP-A) as discussed for immunoblots in Document BC, which method is substantially identical to the method discussed in the above-identified application, and that the ELISA data were taken as discussed in that paper, which method is substantially the same as that of enclosed Exhibit I;

8. That the data in Table 3 of Document BC show that ELISA data (asterisk) based on the recombinant 1-74 residue antigen (identified in Document BC as CAP-A) detected anti-HCV antibodies earlier than did the C-100 antigen-based ELISA in two out of three sera, and that immunoblots using the CAP-A antigen (daggar) detected infection earlier than did the C-100 antigen-based ELISA in four out of five sera;

9. That since the filing of his previous Declaration he has spoken with Dr. Chang Yi Wang about the identity of the

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synthetic core-structural (ST) peptide that was discussed in Paragraphs 20-24 of his previous Declaration;

10. That Dr. Wang is a co-author of Hosein et al., Proc. Natl. Acad. Sci. USA, 88:3647-3651 (1991), a true copy of which was enclosed as Document BA with the previous response, and the first-named inventor of U.S. Patent No. 5,106,726 of record herein;

11. That Dr. Wang fax'd a reply, a true copy of which is enclosed as Exhibit II;

12. That as is seen from enclosed Exhibit II, the core-structural peptide was actually a mixture of two peptides; i.e., VIIIE and IXD of U.S. Patent No. 5,106,726, so that the stated belief of previous Paragraph 20 was partially correct and the true identity of the UBI-ST antigen is now known;

13. That the data of Paragraphs 20-24 of his previous Declaration thus compared an ELISA assay based on the recombinant 1-120 residue protein (CAP) to an ELISA (UBI-ST) using the two overlapping peptides VIIIE and IXD that also encompass the 1-120 region;

14. That the CAP-based ELISA was also carried out following the protocols of enclosed Exhibit I, whereas the UBI-ST ELISA was carried out following the protocol supplied by UBI;

15. That it is now seen that the two antigens, both containing the same region, produced different results, with the recombinant antigen of the present claims providing a superior result;

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16. That the ELISA data reported in previously provided Document BB [Sugitani et al., The Lancet, 339:1018-1019 (1992)] were carried out for others' kits pursuant to the manufacturers' directions, and for the "Capsid" (recombinant 1-120 residue) antigen as discussed in Document BC; and

17. That he further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing on this application.

Date April 20 1993

Alfred M. Prince
Alfred M. Prince, M.D.

Enclosures

EXHIBIT I

HCV CORE ELISA

10-28-90 - Method #2

Materials:

1. Hepatitis C Capsid Protein (PHAGE Lot # NB53P255) in 4M Urea. Source: E. coli (W3110/pGEX7 - Capsid #10)
2. Nunc Immuno MaxiSorp 96 well plates
3. Goat Serum, Gibco Labs
4. Bovine Serum Albumin - Fraction V, MW = 68,000, Boehringer Mannheim
5. 3M H2SO4
6. Sodium Carbonate buffer, pH 9.6 (coating buffer)
7. 0.1 M Sodium Citrate buffer, pH 5.0
8. OPD tablets, Zymed Labs.
9. HRP conjugated Anti Human IgG (Kirkegard & Perry)
10. PBS, pH 7.2
11. 5% Tween 20 in PBS

Procedure:

A. Coating of plates

1. Dilute the protein to 1 ug/ml in coating buffer containing 4M Urea:
For 20 mls of coating buffer - 26 ul of protein
4.2 g Urea
2. Add 100 ul to all wells
3. Cover and let stand overnight at RT
4. Refrigerate plates in a moist chamber and use within 1 week (longer storage will need to be tested in the future)

B. Assay

1. For each plate to be done prepare 40 mls of PBS containing 10% Goat sera (4mls) and 3% BSA (1.2g), and 0.05% Tween 20 (0.4 ml of 5% Tween 20).
This is the diluent for steps 3,5, and 7
2. Wash plate 3X with PBS/Tween 20 (0.05%)
3. Add 150 ul of diluent to each well and block for 2 hrs 37 C. The plate can now remain at room temp until ready to proceed
4. Wash plate 3X with PBS/Tween
5. Prepare a 1:50 dilution of the sera with diluent and add 100 ul to wells. Include a positive and negative control in row 1 as follows:
Row A - Blank
Rows B-D - Neg cont diluted 1:50
Rows E-F - Pos cont diluted 1:50
Rows G-H - Pos cont diluted 1:500
6. Incubate 15 min 37 C
7. Wash plate 5 X, add 100 ul of conj currently used

Kirkegard and Perry 1:2000

8. Incubate 15 min 37 C
9. 10 minutes before incubation is over prepare OPD:
 - 12 ml Citrate buffer
 - 12 ul H2O2
 - 1 OPD tablet
10. Wash plate 5 X, add 100 ul of OPD solution
11. Incubate 20 min RT in the dark.
12. Stop with 50 ul of 3M H2SO4 and read at T490/R630
13. CUTOFF:
 - Human Sera - Ave neg controls + 0.300
 - Chimp Sera - Ave neg controls + 0.200

HCV

EXHIBIT II



UNITED BIOMEDICAL, INC.
25 Davids Drive, Hauppauge, NY 11788 • (516) 273-2828 • Fax: (516) 273-1717

March 2, 1993

Dr. Alfred Prince
New York Blood Center
310 E. 67th Street
New York, NY 10021

Dear Fred:

As per our discussion yesterday, I am sending you a copy of our U.S. Patent #5,106,726 on HCV peptides.

The peptides used in our HCV core/nt EIA are designated VIIIE & IXD as illustrated in Example 15. Their sequences can be found in Claim 22.

I look forward to meeting you and your colleagues in mid-April for a fruitful scientific discussion.

Regards,


Chang Yi Wang, Ph.D.
Chief Scientific Officer

CYW:lk
Encl.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Zebedee et al.)	
Serial No.:	07/616,369)	Attorney Docket
)	PHA-0026P
Filed:	November 21, 1990)	
)	Group Art Unit: 1802
For:	NON-A, NON-B, HEPATITIS VIRUS)	
	ANTIGEN, DIAGNOSTIC METHODS AND)	
	VACCINES)	
Examiner:	D. Wortman)	

SECOND SUPPLEMENTAL RESPONSE

Box Non-Fee Amendments (Pats)
Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

*Official
Copy*

Sir:

This is in further response to the Office Action dated October 5, 1993 to which a previous response was filed on January 28, 1993, a Supplemental Response was filed on February 12, 1993, and a personal interview was held with the Examiner on February 23, 1993.

RESPONSE

Reconsideration of the above-identified application is respectfully requested in view of the previously filed Response, Supplemental Response and the present, Second Supplemental Response.

The Examiner is thanked for the courtesies extended and comments made to Dr. Helting and counsel during their interview. This Response will address those comments.

Claims 35-46 are before the Examiner.

Inasmuch as there was no discussion during the interview of the previously outstanding rejection under 35 U.S.C. §112, first and second paragraphs, that was responded to in the Response mailed January 28, 1993, no discussion will be had here on those issues. Rather, the present response will deal with the alleged anticipation/obviousness issues and the previously filed Declaration of Dr. Prince.

A. The Second Prince Declaration

Enclosed herewith is a true copy of a Second Declaration of Alfred M. Prince, M.D., a named inventor herein. The original of this Declaration is being filed with the parental application, Serial No. 07/573,643. Dr. Prince's prior Declarations in both this application and the parental application were substantially identical as to the comments raised during the interview. It is therefore believed that a second, original, Declaration is not needed here. However, should the Examiner request such a Declaration, it can be provided.

Dr. Prince's enclosed, Second Declaration points out (Paragraphs 2-5) that the data of Paragraphs 6-10 of his previous Declaration were taken by ELISA. The procedures provided with the commercial kit (C-100 antigen) were used, and a protocol for the ELISA using a recombinant is enclosed therewith. Thus, the data of Dr. Prince's previous Paragraphs 6-10 compared ELISA to ELISA, and showed an ELISA based upon a claimed recombinant to

outperform the then industry standard, commercial C-100 antigen-based ELISA.

Paragraphs 6-8 of Dr. Prince's present Declaration point out that ELISA and immunoblot assays were also carried out as discussed in previously submitted Document BC using a recombinant 1-74 residue antigen, with the details for each of those assays being given in Document BC. Present Paragraph 8 points to Table 3 of Document BC in showing that an ELISA based on that recombinant 1-74 residue antigen also outperformed the industry standard C-100 antigen-based ELISA assay for two of three sera, whereas an immunoblot based on that same recombinant outperformed the C-100 antigen-based ELISA with four of five sera.

Paragraphs 9-15 of Dr. Prince's present Declaration discuss the identity of the antigen of the UBI ELISA kit he obtained denominated "ST" and the data obtained therewith, as compared to an ELISA based on a HCV recombinant 1-120 residue antigen. The results of those ELISA assays were discussed in Paragraphs 20-24 of Dr. Prince's prior Declaration. The present Declaration also discusses how those ELISA assays were done.

As is seen from Dr. Prince's present Paragraphs 9-15 and Exhibit II enclosed therewith, Dr. Wang has now identified the peptide antigen used in the "ST" ELISA as being both of peptides VIIIE and IXD of her U.S. Patent No. 5,106,726. Thus, the results discussed in the previous Prince Declaration Paragraphs 20-24 compared ELISA to ELISA with a recombinant

antigen and synthetic peptides covering the exact same region. Those results also showed a method using a recombinant antigen to be superior.

Paragraph 16 of Dr. Prince's present Declaration discussed how the ELISA's using others' kits and an ELISA based on the recombinant 1-120 residue antigen of previously submitted Document BB were carried out.

The immunoblot data of the application and the ELISA and immunoblot data of Dr. Prince's previous and present Declarations show the following:

(a) a method using immunoblots with a recombinant 1-74 residue antigen detected HCV infection earlier than did an ELISA assay based on the C-100 non-structural antigen (application Tables 2, 3, 4, 5 and 6; 2nd Declaration Par. 6-8; Document BC, Table 3, dagger data);

(b) ELISA comparisons between a recombinant antigen having the 1-74 residue sequence and C-100 showed the method using the 1-74 residue recombinant to be superior (Document BC, Table 3, asterisk data);

(c) ELISA method comparisons using the C-100 commercial antigen and the 1-120 residue recombinant showed the recombinant antigen to be superior (1st Declaration Par. 6-10; 2nd Declaration Par. 2-5);

(d) ELISA method comparisons using Dr. Wang's synthetic peptides VIIIE and IXD ("ST" kit) and a recombinant 1-120 residue of the claims as antigens showed a method using a

recombinant antigen to be superior to use of synthetic peptides covering the same region as antigen (1st Declaration Par. 20-24; 2nd Declaration Par. 9-15); and

(e) ELISA method data using a recombinant 1-120 residue antigen provided the same results as an ELISA method containing synthetic peptides from both structural and non-structural proteins (UBI-HCV) (1st Declaration Par. 16-19; 2nd Declaration Par. 16; Document BB).

Thus, the data provided show an assay method using a recited recombinant antigen to be: (a) superior to the C-100 antigen-based ELISA by ELISA and immunoblot, (b) superior to an antigen containing a combination of synthetic peptides covering the same region by ELISA, and (c) comparable to an ELISA using synthetic antigens from both structural and non-structural regions.

B. The Art-Based Rejections

Each of the art-based rejections was tied to the disclosures of the Wang et al. U.S. Patent No. 5,106,726, hereinafter referred to as "Wang", and each of those rejections was dealt with in the prior response. This response will therefore be limited to the unexpected results discussed in the application using a recombinant antigen having the sequence of positions 21-40, as recited in claim 35.

The Response mailed January 28, 1992 (the previous Response) noted that the data of the Wang disclosure compared assay results using an ELISA format with a synthetic peptide as

antigen. Those results were compared to Wang's synthetic peptide IIID, whose ELISA results were compared with an ELISA based on the C-100 antigen.

When ELISA results for peptides VIIIE and IXD were compared to those for peptide IIID (Table 7), and thus to an ELISA with C-100, the best that was observed was a result that was 98.6 percent as good as a C-100 antigen-based assay. The data of Table 7 (pages 74-76) of the present application relate to immunoblot data using antigens referred to as CAP-N, CAP-A, CAP-B and CAP-C that were recombinant antigens corresponding to positions 1-74, 1-20, 21-40 (claimed here), and 41-60 of the HCV capsid, structural protein.

The immunoblot data of Table 1 (page 5465) of Document BC (Nasoff et al.) that accompanied the January 28, 1993 response showed that the recombinant containing the sequence of residues 1-74 (there identified as CAP-A) was the only sequence from the group of residues 1-74, 69-120 (there called CAP-B) and 121-321 (there called CAP-C) that bound anti-HCV antibodies.

The data of Table 2 of Document BC augment the similar data of Table 7 herein and show that the short sequence region most effective for binding anti-HCV antibodies is that claimed herein as an antigen; i.e., positions 21-40 (there called CAP-2), with the amino-terminal region having positions 1-20 (called CAP-1) exhibiting poorer binding, and positions 41-60 being responsible for almost no antibody binding, as is also shown in Table 7 herein.

It is respectfully submitted that nothing in the Wang disclosures teaches a worker of ordinary skill to discard the N-terminal nineteen residues and the C-terminal eighty residues of the capsid protein (or the twenty C-terminal residues of Wang's peptide VIIIE) to arrive at a useful recombinant antigen containing residues 21-40. The prior Action asserted that deletion of the about 40 N-terminal residues of a Wang synthetic caused a decrease in binding titer. That assertion was made based on the data of Wang's Table 7.

The present claims recite a recombinant containing the sequence of positions 21-40. It is submitted that Wang's data of Table 7 show Wang's N-terminal nineteen residues to be of great import to her sequences in that without them, the titer goes down almost 30 percent.

The data of Wang's Fig. 11-1 must also be considered. There, three of the four samples showed the N-terminal nineteen residues to be quite important to the titer achieved. Wang also selected a peptide containing that nineteen N-terminal sequence for her further assays; i.e., peptide VIIIE.

It is thus submitted that Wang's teachings, as a whole, suggest to a skilled worker that the N-terminal nineteen residue sequence should be present. That sequence is absent from a claimed recombinant.

It is also submitted that Wang teaches that residues substantially beyond position 40 should also be present. There

are only teachings of such peptides, and no teachings to the contrary.

It must also be remembered that the data for Wang's synthetic peptides in Fig. 11-1 are all ultimately related to an ELISA based on the commercial C-100 antigen. The data of Fig. 11-1 were all inferior to those obtained using the C-100 antigen.

The present application teaches that using immunoblot assays, a recombinant antigen containing the sequence of positions 1-74 (application CAP-N; Document BC CAP-A) consistently outperformed that commercial ELISA. The data in application Table 7 and Document BC Table 2 show that an immunoblot method using a claimed recombinant provided very similar results to those using a CAP-N antigen. A slight preference may be shown in those data for a claimed method to be useful for distinguishing acute from chronic infection, and that direction is being pursued.

The data in Table 3 of Document BC show that the results observed with immunoblots using the recombinant 1-74 residue antigen versus a C-100 antigen-based ELISA are also generally found when the method using a recombinant 1-74 residue antigen is practiced in an ELISA format. There is no evidence of record that indicates those findings would also not apply to an ELISA-type assay using a claimed method.

It is again submitted that Wang alone or in combination with any other disclosure neither teaches nor suggests the


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presently claimed subject matter. It is thus submitted that the claimed subject matter is patentable.

No further fee or petition is believed necessary. However, should any further fee be needed, please charge our Deposit Account No. 04-1644, and deem this paper the required Petition.

Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381

Enclosure
copy of Second Declaration of Alfred M. Prince, M.D.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
37-516,385	4/22/1998	ZEBEDEE	PH00034

WIRTSCHAFTS-EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED: 07/13/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined

☒ Responsive to communication filed on:

☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. § 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892. 2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474. 6. ☐

Part II SUMMARY OF ACTION

1. ☒ Claims 35-46 are pending in the application.

Of the above, claims .. are withdrawn from consideration.

2. ☒ Claims 1-34, 47-53 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 35-46 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____ Under 37 C.F.R. 1.84 these drawings are ☐ acceptable ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation): _____

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has: ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

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Claims 35-46 are under examination at this time. Claims 35 and 37 were amended in Paper No. 15.

Applicant has submitted five articles as well as a form PTO 1449, recorded as Paper No. 17, on which those articles are listed. In addition, Applicant has submitted another PTO 1449 with references attached to the Supplemental Response which is recorded as Paper No. 19. All of these references have been placed in the file and considered to the extent they bear on Applicant's remarks but have been crossed off the forms 1449 because neither information disclosure statement complies with 37 CFR 1.97(c).

Claims 36-38 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 36-38 are unclear because each recites "... protein has an amino acid residue sequence contained in ..." and it cannot be determined from that language whether Applicant intends to claim the entire portion of the sequence that is derived from NANBV or some portion of it. As recited, the claim encompasses just two adjacent amino acid residues which would constitute a sequence. In addition, the specification is not enabling for portions of the NANBV sequence since no guidance is given for selecting smaller peptides for use in the instant method.

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Applicant has amended Claims 35 and 37 and urges that taken in the proper context the claims should be interpreted as having the entire recited sequence.

5 This argument is not convincing and the amendments to the claims have not provided claims that are both clear and enabled. Claims 36-38 still read "has an amino acid residue sequence contained in ..." which one of ordinary skill in the art would reasonably interpret as having any part of the amino acid in common with the sequence recited. As previously discussed, the
10 specification is not enabled for all the sequences encompassed by that language because Applicant has not provided any guidance for selecting, making recombinantly, and using any NANBV recombinant proteins or polypeptides except for those specifically exemplified and it would require undue experimentation for one of
15 ordinary skill in the art to select, make and use other recombinant polypeptides from the countless possibilities.

Claims 36 and 38 rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 36
20 and 38 do not further limit Claim 35 since they are drawn to amino acid sequences that do not appear in Claim 35 as amended in Paper No. 15.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under
25 this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35

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U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 35 and 37 as amended and Claims 36 and 38-46 are rejected under 35 U.S.C. § 103 as being unpatentable over Wang in view of Kuo et al., both references of record. Wang teaches assaying sera for antibodies against HCV (NANBV) using solid phase coated with peptides that include amino acid residue sequences as instantly claimed (see Wang, Example 14 and Table 7, especially peptide VIIIE) but teaches synthetic peptides rather than the recombinants as instantly claimed. Kuo teaches production of an HCV recombinant fusion protein for use in immunoassays. It would have been obvious to one of ordinary skill in the art to produce the HCV peptide of Wang recombinantly as taught by Kuo in order to gain the advantages of producing peptides by recombinant means, e.g., to obtain a stable, plentiful supply of peptides that are free of contamination with other HCV antigens and to use them in immunoassays with reasonable expectation for success because both Kuo and Wang successfully use HCV peptides to detect antibodies in sera. It is noted that "including" as recited in Claim 35 and "has" as recited in Claim 36 encompass any common amino acid sequence; Applicant has indicated on the record (Paper No. 15, paragraph bridging pp. 2-3) that the language of Claim 35 reads on recombinant antigens that include the sequence 21-40, as do CAP-N (1-74), CAP-B (20-41), and entire capsid 1-120. Thus the VIIIE peptide sequence of Wang clearly reads on the claimed antigen

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sequence. Even if the instant sequences were recited more narrowly, they would have been obvious over Wang because the results represented in Table 7 clearly shows immunoreactivity for all the core sequences shown (see Table 7, column labeled "%

5 Immunoreactivity," especially results obtained with peptides VIIIE, VIIID, VIIIC, VIIIB, VIIIA).

Applicant has argued:

- 1) The present claims are drawn to recombinant polypeptides and Wang uses synthetic polypeptides.
- 10 2) Different results are obtained with the instant recombinants than with similar synthetic polypeptides, and points to results obtained in Wang using peptides I and III to support the contention that the same sequence can behave differently in different peptides in terms of binding antibodies. Applicant
15 further contends that the VIIIA-VIIID peptides of Wang are not as effective as IIID and are thus less effective than C100, and points to specification pages 69-76 as evidence that the instant CAP-B antigen "out-performed" a kit using C100. Applicant has
20 also submitted Declarations from Dr. Prince showing results from comparing Applicant's recombinant 1-74 antigen and Applicant's 1-120 antigen with C100 and Wang's peptides VIIIE and IXD. In Paper No. 20, Applicant points to results obtained by Wang to show that deleting the N-terminal nineteen residues and the C-terminal eighty residues of the capsid protein would not have
25 been obvious.

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3) Recombinants are less desirable than synthetic antigens because they are more difficult to purify.

4) That Kuo used yeast recombinant antigens and not E. coli.

Applicant's arguments and supporting documents have all been considered but not found persuasive for the following reasons:

With respect to points 1), 3) and 4), Wang does not teach recombinant HCV polypeptides but Kuo does. In addition, Applicant's claims are not limited to recombinant HCV polypeptide produced in E. coli.

With respect to point 2), Dr. Prince's Declarations have been fully considered but are not found persuasive for reasons which depend on claim interpretation. Dr. Prince's Declaration is not commensurate in scope with the claims because the Declarations concern only recombinant GST fusion protein with 1-74 antigen and Applicant's 1-120 antigen. However, if, as Applicant has stated, Claim 35 is intended to read on those antigens, the question of double patenting is raised because the claims of parent application 07/573643 would be drawn to the same invention. However, if the claims are interpreted to read on just the 21-40 fusion protein antigen, Dr. Prince's Declarations are not seen to be relevant because that antigen is not mentioned in the Declarations. The specification at page 74, Table 7, cited by Applicant, shows results with the CAP-B fusion protein produced recombinantly in E. coli as compared to CAP-N, CAP-A, and CAP-C fusion proteins and indicates that CAP-B works almost

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as well as CAP-N in detecting antibodies in acute sera but not as well as CAP-N in detecting antibodies in chronic sera, which Applicant holds to be an unexpected result. These comparisons are not persuasive with respect to results obtained with the CAP-B fusion protein because the instant claims are not limited to that particular antigen.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

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Any inquiry concerning this communication should be directed
to Examiner Donna C. Wortman at telephone number (703) 308-1032.

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DW
Donna C. Wortman, Ph.D.
July 8, 1993

Esther Kepplinger

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ESTHER L. KEPPLINGER
SUPERVISORY PATENT EXAMINER
GROUP ART UNIT 1802

File History Report

☐

Paper number _____ is missing from the United States Patent and Trademark Office's original copy of the file history. No additional information is available.

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The following page(s) **PTO-1449** of paper number _____ is/are missing from the United States Patent and Trademark Office's original copy of the file history. No additional information is available

Additional comments: _____



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RESPONSE UNDER 37 C.F.R. 116
EXPEDITED PROCEDURE
EXAMINING GROUP 1802

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 07/616,369) Attorney Docket
Filed: November 21, 1990) PHA-0026P
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES) Group Art Unit: 1802
Examiner: D. Wortman)

AMENDMENT UNDER 37. C.F.R. §1.116

Box AF
Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action dated July 12, 1993,
please amend the above-identified application as follows.

IN THE CLAIMS

Please cancel claims 36, 37 and 38.

Please amend claim 35 as follows:

35. (Three-Times Amended) A method of assaying a body
fluid sample for the presence of antibodies against NANBV, which
method comprises:

a) forming an immunoreaction admixture by
admixing said body fluid sample with a recombinant NANBV
[structural] fusion protein [or portion thereof, said recombinant
protein] having the [or portion including an] amino acid residue
sequence represented by the sequence [contained in] of SEQ. ID.
NO. [1] 4 [from residue 21 to residue 40];

b) maintaining said immunoreaction admixture for
a time period sufficient for any of said antibodies present to

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immunoreact with said recombinant NANBV [structural] fusion protein [or portion] to form an immunoreaction product; and

31 c) detecting the presence of any of said immunoreaction product formed and thereby the presence of said antibodies.

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the discussion that follows is respectfully requested.

Claim 35 has been amended as discussed below and claims 36, 37 and 38 cancelled. Claims 35 and 39-46 are before the Examiner.

I. The Amendments

Claims 36, 37 and 38 have been cancelled to speed prosecution.

Claim 35 has been amended to recite use only of the GST-fusion protein that contains the position 21-40 portion of the NANBV capsid protein for which data are provided in the application. This fusion protein is referred to as CAP-B in the specification and as CAP-2 in document BC.

The word "including an" have been replaced with the words "having the". The claim has also been amended to delete the phrase "contained in" and replace that phrase with "of".

Support for these amendments can be found throughout the specification. Further specific support can be found at least at page 5, lines 17-26; page 10, line 22 through page 11, line 6; page 24, line 17 through page 28, line 2; and the examples such as page 62, line 33 through page 63, line 16 and the text surrounding Table 7 at pages 74-75.

It is thus seen that no new matter has been added.

II. THE ACTION

A. Compliance with 37 C.F.R. §1.97(c)

The fee required under §1.97(c) is enclosed pursuant to the above section and §1.17(p). It is noted that the last paragraph of the two Supplemental Responses requested that any further fee be charged to counsel's Deposit Account. It is thus believed that the requirements of Section 1.97(c) have been met.

B. Rejection Under 35 U.S.C. §112, First and Second Paragraphs

Claims 36-38 were rejected as allegedly failing the description requirement of the first paragraph and/or allegedly failing to particularly point out and distinctly claim applicants' invention. It is believed that this rejection is moot as to cancelled claims 36, 37 and 38.

C. Rejection Under 35 U.S.C. §112, Fourth Paragraph

It is believed that this rejection is also moot in view of the cancellation of rejected claims 36 and 38.

D. Rejection Under 35 U.S.C. §103

The pending claims were rejected as allegedly obvious over the disclosures of Wang in view of Kuo, both of which have been discussed several times in this prosecution. This rejection is respectfully traversed.

The Action asserts that Wang teaches use of synthetic HCV "peptides that include amino acid residue sequences as instantly claimed ..." as antigens for solid phase assays. Actually, at column 29, lines 32-37, Wang teaches her peptides to be useful in not only solid phase assays, but also in an "enzyme immunodot assay, an agglutination based assay, or other well-known immunoassay devices." The Action asserts the prior use of "including" encompasses any overlapping sequences and that narrowed sequences would still be obvious from Wang. The Action

states that Wang does not teach use of recombinant peptides, but that Kuo teaches use of recombinant technology with other HCV proteins so that it would have been obvious to use Kuo's technique to make a Wang peptide.

The paragraph bridging Wang's columns 23 and 24 teaches several advantages and distinctions of her synthetic peptides over "biologic" materials for use in the assays contemplated. Among those advantages are the high yield, gram quantity amounts of synthetic peptide that can be obtained by which

"a reproducible antigen of high integrity with consistent yields [can be produced]. The presence of other antigens from biological systems precludes such reproducibility." [Column 23, lines 56-61.]

That same paragraph continues by saying that even

"more importantly, non-specific reactivities seen in uninfected individuals are likely to be due to the heterogeneity of the preparations used for assay. This is particularly true for assays using biologically based immunoadsorbents." [Column 23, lines 61-65.]

The remainder of that paragraph discusses biologically based materials isolated from hosts. However, at column 5, lines 29-55, Wang also touts how wonderful synthetic peptides are for assays, citing to her U.S. Patents No. 4,735,896 and No. 4,879,212, and asserting "superior sensitivity, excellent specificity, ..." and viral differentiability for such materials, "thus overcoming many of the existing problems with biologically-derived tests based on either viral lysate or recombinant DNA-derived protein." (Column 5, lines 49-55; emphasis supplied.)

It should thus be clear that the claimed recombinants are among the "biologically based immunosorbents" whose use Wang's synthetic peptides were designed to replace.

As pointed out in In re Fine, 5 USPQ2d 1596, 1499 (Fed.Cir. 1988), one tests obviousness by what the combined

teachings of the references would have suggested to those of ordinary skill in the art. Obviousness cannot be established by combining teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. See, also, In re Jones, 21 USPQ2d 1941, 1944 (Fed.Cir. 1992).

Here, Wang teaches that one should not use biologically based antigens for several reasons, noted before. That is a teaching contrary to the Action's position that is from the art relied-on for this rejection. The combination is therefore improper, and this rejection should be withdrawn.

The Kuo teaching utilizes recombinant technology with a group of HCV proteins different from those claimed here. It has no teaching as to the present structural proteins, nor as to what primers or other materials to use to obtain the claimed recombinant antigen. Kuo also therefore teaches away from the Action's combination.

Thus, there is motivation in the relied-on art against making the Action's combination, and there is no teaching in either document as to how to make that which is claimed. The present basis for rejection is thus submitted to be a hindsight reconstruction, and should be withdrawn.

A similar situation arose in the recently published decision in In re Bell, 26 USPQ2d 1529 (Fed.Cir. 1993). There, a DNA sequence of a known protein was claimed. One relied-on reference taught the protein sequence, and the other taught a general method of gene cloning. The Examiner and Board held the claimed DNA to be obvious. The Court disagreed.

It is submitted that the presently claimed subject matter that is now limited to the CAP-B construct is patentable over the asserted combined teachings of Wang and Kuo, even though

it is maintained that those teachings are improperly combined in the Action. It is also submitted that no issue of double patenting as to co-pending application Serial No. 07/575,643 is raised from the present claims.

As to the non-obviousness issue, it has previously been discussed that the data of Table 7 herein illustrate that the CAP-B (21-40) recombinant fusion protein is almost as good an antigen as is the CAP-N (1-74) recombinant fusion protein that was shown to be a better antigen in both ELISA and immunodot formats than the C-100 construct (document BC). It will also be remembered that the data of Wang's Table 7 showed each of her synthetic peptides, including her best peptide or VIII E, to be a poorer antigen than the C-100 material.

Thus, a recombinant fusion protein construct whose antigenic peptide portion is about one-third the length of a Wang synthetic peptide also outperformed the C-100 antigen. That result was unexpected, not predicted and not obvious.

Still further work has been carried out on the presently claimed subject matter in view of the comments made in the present Final Office Action. That work was carried out by Dr. Torsten B. Helting, whose Declaration is enclosed.

As will be seen from the enclosed Declaration, solutions containing the recombinant 1-120 protein (Preparation A) and a recombinant 21-40 fusion protein (Preparation B) were prepared and isolated. The fusion protein (Preparation B) was treated with thrombin to cleave the fused protein portion and thereby prepare a solution containing the free 21-40 peptide (Preparation C).

Immunoreactivities of the proteinaceous materials present in Preparations A, B and C were then assayed by an immunodot technique using four different concentrations of each

I think that
Prep B is the
best C is prepared

of the three preparations and four sera known to immunoreact with the capsid protein. The results of that study (Fig. 3) showed the recombinant 1-120 and recombinant 21-40 fusion protein antigens to exhibit similar good immunoreactivities, whereas the free peptide, Preparation C, showed almost no immunoreactivity.

Dr. Helting's conclusions from those results were:

(i) the pattern of reactivity of an amino acid residue sequence seen within the context of one molecular framework of a recombinant protein or fusion protein cannot be used to predict what reactivity pattern might emerge if the same sequence is assayed in a molecular environment that lacks the fused protein portion;

(ii) the free residues 21-40 peptide of Preparation B is similar to entities derived by chemical synthesis, and in this study such a peptide is clearly inferior to maintain the immune reactivity it possesses within the context of the larger protein structure of the recombinant whole protein or fusion protein;

(iii) in view of the previously shown similarities between the 1-120 recombinant and the recombinant 1-74 fusion protein, the immunodominant domain for the HCV capsid lies in the region between position 1 and position 74 of the protein;

(iv) in view of the similar reactivities shown here between the 1-120 recombinant and the recombinant 21-40 fusion protein, that immunodominant region is most likely centered at about positions 21-40 of the capsid;

(v) it is his belief in view of the data in the subject application, its co-pending parental application Serial No. 07/573,643, and the submitted articles and data, including those data herein, that the longer chains of amino acid residues present in the recombinant 1-74 fusion protein, the recombinant 21-40 fusion protein and recombinant 1-120 protein on one side or

the other of the immunodominant domain function to optimally present the immunodominant domain to the antibodies; and

(vi) that optimal presentation is not achieved with the smaller polypeptides disclosed in the Wang patent.

It is thus seen that a claimed fusion protein whose antigenic portion is about one-third the length of Wang's best peptide (VIII E) exhibited an immunoreactivity about equal to that of the whole recombinant, whereas the free peptide antigen itself showed almost no reactivity. That result could not be predicted a priori, let alone from the Wang disclosures.

It is thus again submitted that the presently claimed subject matter is patentable over the art of record.

III. SUMMARY

Claims 36, 37 and 38 have been cancelled. Claim 35 has been amended to recite use of the CAP-B recombinant fusion protein having an antigenic peptide portion whose amino acid residue sequence is that of positions 21-40 of the NANBV capsid protein. Each basis for rejection has been overcome or otherwise been made moot. Further evidence of the unobvious results of a claimed method have been presented in view of the presently outstanding Action.

It is therefore believed that the subject application is in condition for allowance. An early notice to that effect is earnestly solicited.

The Examiner is urged to phone the undersigned should she have any questions or suggestions for further amendments that may speed allowance.

No further fee or petition is believed necessary. However, should any further fee be needed, please charge our

Serial No. 07/616,369



Deposit Account No. 04-16427, and deem this paper the required
Petition.

Respectfully submitted,

By *Edward P. Gamson*
Edward P. Gamson, Reg. No. 29,381

Enclosures

Declaration of Dr. Torsten B. Helting
Fee Under 37 C.F.R. §1.97(c)

CERTIFICATE OF MAILING

I hereby certify that this Amendment Under 37 C.F.R.
§1.116, together with the stated enclosures, is being deposited
with the United States Postal Service as First Class Mail,
postage prepaid, in an envelope addressed to: Box AF, Hon.
Commissioner of Patents and Trademarks, Washington, D.C. 20231 on
October 12, 1993.

Edward P. Gamson

#2
1049-9



THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 07/616,393) Attorney Docket
Filed: November 21, 1990) PHA 0026P
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: D. Wortman)

DECLARATION OF DR. TORSTEN B. HELTING

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

DR. TORSTEN B. HELTING, Declares:

1. That he was the President of Pharmacia Genetic Engineering, Inc. (Phage) of La Jolla, California, an original co-assignee of the subject application;
2. That Phage, since the filing of this application, has been dissolved and its assets assumed by Pharmacia Biosystems, Inc. of Piscataway, New Jersey;
3. That he was intimately associated with the research that underlay the present application and is co-pending parent application Serial No. 07/573,643 filed August 27, 1990;
4. That he has continued to be involved with research related to the claimed subject matter since the dissolution of Phage;

10/2/93
C. J. [signature]

5. That he has read and is familiar with the Final Official Action dated July 12, 1993;

6. That because of the points raised in that Action, he carried out the further studies discussed below;

7. That free capsid protein residue 1-120 was isolated from induced E. coli cultures transformed with a plasmid encoding the amino acid sequence from position 1 through position 120 of SEQ ID NO:1 herein, and that a solution containing the free recombinant capsid portion was subsequently isolated via gel and ion exchange chromatography;

8. That the purified capsid was adjusted to an $OD_{280\text{ nm}}$ equal to 0.01 by diluting with 20 mM Tris-HCl buffer, pH 7.5 containing 500 mM NaCl (TBS), and labeled Preparation A;

9. That the GST-21-40 fusion protein was isolated from induced E. coli cultures transformed with the plasmid GST-2T-CAP-B of this application; the bacteria being harvested by centrifugation and subsequently being treated with lysozyme and ultrasonication, differential centrifugation, Sepharose S-300 gel chromatography and affinity chromatography on a glutathione-agarose affinity column (Cat. #9761, Sigma). The latter column was washed with 0.02M Tris-HCl buffer, containing 0.2 M NaCl and the purified GST-21-40 fusion protein was eluted from the affinity column by using the same buffer containing reduced glutathione (5 mg/ml) (enclosed Fig. 1). The eluate (Peak 2, Fig. 1, attached) was subsequently dialyzed against 0.05 M Tris-HCl, pH 7.2 containing 0.15 M NaCl and 2.5 mM $CaCl_2$;

10. That five ml of the dialyzed preparation, having an OD_{280} equal to 0.06, were retained as a parent GST-21-40 preparation during the incubation of an equal volume (5 ml) with human thrombin (100 U/ml, 25 μ l) at room temperature for 60 minutes. The resulting thrombin digest was then applied to a column (0.8x5 cm) of the glutathione-agarose affinity resin. The flow-through was collected and the column washed to elute the released peptide in a total volume of 10 ml (i.e. a 1:2 dilution of the starting material (enclosed Fig. 2, peak 1; prep I). The free peptide was thus separated from the GST carrier, which still bound to the affinity resin and was eluted with buffer containing reduced glutathione (5 ^{mg/}~~m~~/ml* Fig. 2, peak 2);

11. That the parent GST-21-40 preparation was also diluted 1:2 (5 ml adjusted to 10 ml), thus providing an equivalent molar concentration of free peptide and fusion protein (prep. II).

12. That subsequently, to adjust all preparations to an approximate OD_{280} equal to 0.01 (or equivalent), a 1:3 dilution of prep. I in TBS was prepared and labeled Preparation B;

13. That likewise, a 1:3 dilution of prep. II, described above was prepared by addition of TBS and labeled Preparation C. Thus, Preparations B and C constitute equivalent molar concentrations of the 21-40 peptide, present in Preparation B in free form, whereas linked to GST in Preparation C.

14. That the recombinant capsid preparations were subsequently compared as antigens by adsorption onto

nitrocellulose membrane at four different concentrations and subsequently incubated with four different capsid reactive HCV sera to investigate the relative immune reactivity as follows:

(a) A sheet of nitrocellulose membrane (Sigma Cat. #N8017) was wetted with TBS and mounted in a Biorad Biodot microfiltration apparatus (Cat. #170545). In each row of 12 wells, the antigen-containing samples were applied as follows:

Well	Preparation	Dilution in TBS	Volume per Well
1	A	Neat	0.1
2	A	1:5	0.1
3	A	1:25	0.1
4	A	1:125	0.1
5	B	Neat	0.1
6	B	1:5	0.1
7	B	1:25	0.1
8	B	1:125	0.1
9	C	Neat	0.1
10	C	1:5	0.1
11	C	1:25	0.1
12	C	1:125	0.1

(b) After application of the samples and blocking with 1 percent bovine serum albumin (BSA) in TBS buffer, the wells were washed with TBS containing 0.1 percent Tween 20 (TTBS), and the nitrocellulose sheet removed and dried over P_2O_5 overnight;

(c) Strips containing the 12 samples were cut and subjected to an immunoreaction as follows:

(i) Using a Biorad mini-incubation tray, (Cat # 170-3902), to each of four

troughs were added 1 ml of TTBS containing 1 percent BSA and 10 μ l of a random member of a serum reference panel known to react with the structural region of HCV (Ortho Riba II test). Each trough received one strip, each strip containing the three antigens applied in four different concentrations as shown in the table above;

(ii) After incubating for three hours at 30°C on an orbital shaker, the liquid in each trough was aspirated and the strips washed 5x with phosphate buffered saline containing 0.1 percent Tween 20. Subsequently, blotting grade anti-human IgG-alkaline phosphatase conjugate (Biorad, Cat. #170-6521) diluted 1:1000 in fresh TTBS ^{containing 1 percent BSA} (1.5 ml) was added and the incubation continued for an additional 60 minutes. After removal of the enzyme conjugate and five washes with PBS Tween, the strips were developed by adding the BCIP/NBT (Biorad Cat. #170-6539, 170-6532, respectively) substrate in accordance with the manufacturer's instructions, and incubating for 20 minutes. The reaction was terminated by washing the strips with water and drying;

15. That Fig. 3 shows a photocopy of the mounted strips obtained with those four random sera known to react with the HCV structural protein region, the original of those strips and Figs. 1 and 2 being supplied with his Declaration in co-pending application Serial No. 07/573,643, filed August 27, 1990;

16. That although the immune reactivity shows the expected variation depending on the serum used, the results show a consistent pattern of reactivity, in three out of four sera down to a dilution of 1:125 when using a claimed recombinant GST-21-40 fusion protein or the recombinant 1-120 protein for application to the membrane;

17. That by comparison, the isolated free peptide (residues 21-40, Preparation B) derived from Preparation C shows an almost negligible level of activity under identical conditions;

18. That it is concluded:

(i) the pattern of reactivity of an amino acid residue sequence seen within the context of one molecular framework of a recombinant protein or fusion protein cannot be used to predict what reactivity pattern might emerge if the same sequence is assayed in a molecular environment that lacks the fused protein portion;

(ii) the free residues 21-40 peptide of Preparation B is similar to entities derived by chemical synthesis, and in this study such a peptide is clearly inferior

to maintain the immune reactivity it possesses within the context of the larger protein structure of the recombinant whole protein or fusion protein;

(iii) in view of the previously shown similarities between the 1-120 recombinant and the recombinant 1-74 fusion protein, the immunodominant domain for the HCV capsid lies in the region between position 1 and position 74 of the protein;

(iv) in view of the similar reactivities shown here between the 1-120 recombinant and the recombinant 21-40 fusion protein, that immunodominant region is most likely centered at about positions 21-40 of the capsid;

(v) it is his belief in view of the data in the subject application, its co-pending parental application Serial No. 07/573,643, and the submitted articles and data, including those data herein, that the longer chains of amino acid residues present in the recombinant 1-74 fusion protein, the recombinant 21-40 fusion protein and recombinant 1-120 protein on one side or the other of the immunodominant domain function to optimally present the immunodominant domain to the antibodies; and

(vi) that optimal presentation is not achieved with the smaller polypeptides disclosed in the Wang patent;

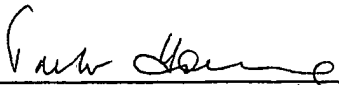
19. That he further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

Serial No. 07/616,393

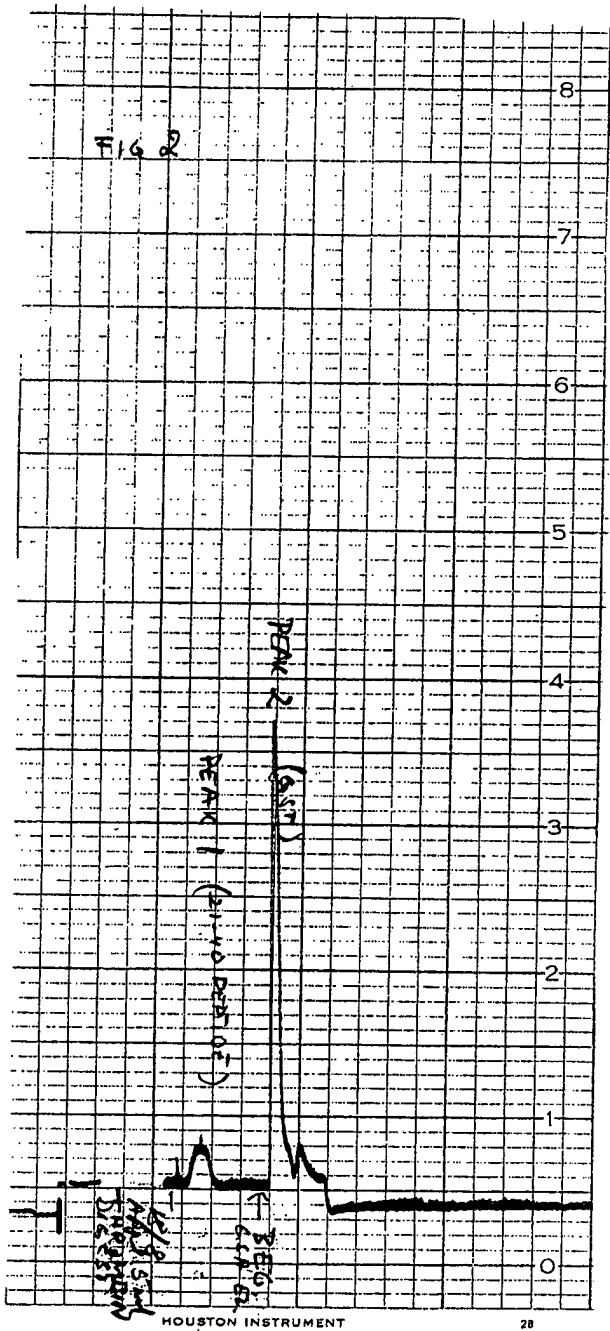
-8-

imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing on this application.

October 8, 1993
Date


Dr. Torsten B. Helting

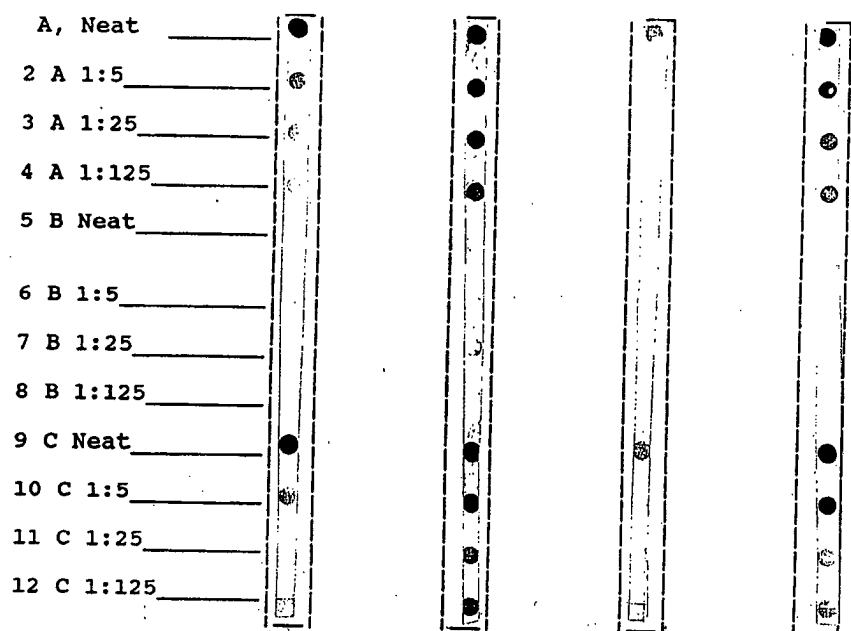
Enclosures



Dot Blot Analysis

Date: Aug 18 1993
Ref. NR 2 PLT
DOT BLOT PREP A-C

Antigen:



Serum ID:

M34727

M34890

9748

MRB3F3



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/616,369	11/21/90	ZEBEDEE	S PHA0026

18N1/1101
DRESSLER, GOLDSMITH, SHORE,
SUTKER & MILNAMOW, LTD.
11300 SORRENTO VALLEY RD, STE 200
SAN DIEGO, CA 92121

WORD NUMBER	
ART UNIT	PAPER NUMBER
1802	24

DATE MAILED:

11/01/93

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

- a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection
- b) ☒ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 10-12-93 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and/or specification will not be entered and the final rejection stands because:
- ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
 - ☐ They raise new issues that would require further consideration and/or search. (See Note).
 - ☐ They raise the issue of new matter. (See Note).
 - ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
 - ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.
3. ☒ Upon the filing an appeal, the proposed amendment ☒ will be entered ☐ will not be entered and the status of the claims will be as follows:

Claims allowed: _____
Claims objected to: 35,39-46
Claims rejected: _____

However;

☒ Applicant's response has overcome the following rejection(s): rejections under 35 USC 112

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because See attached
5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other P.T.O. 1449 copy attached

The Information Disclosure Statements previously submitted as Paper No. 17 and attached to Paper No. 19 have now been made of record and copies are attached to this Advisory Action.

5 The proposed amendment cancelling Claims 36, 37, and 38 and amending Claim 35 would overcome rejections of Claims 36-38 previously made under 35 USC 112.

10 The proposed amendment clarifying and narrowing the scope of Claim 35 to recite only the recombinant fusion protein GST-21-40 (subject matter previously recited in Claim 37), Applicant's remarks, and the Declaration of Dr. Helting have been considered but have not been found persuasive of unobviousness over Wang in view of Kuo et al.

15 Dr. Helting's declaration presents data comparing the binding of equivalent molar concentrations of recombinant capsid protein 1-120, Preparation A; recombinant free peptide 21-40, Preparation B; and recombinant fusion protein GST-21-40, preparation C to four different capsid reactive HCV sera. The results show that recombinant capsid protein 1-120 is most reactive, that recombinant fusion protein GST-21-40 is almost as reactive as 1-120, and that GST-21-40 is considerably better than free 21-40. However, the declaration does not provide a direct comparison of the closest prior art with the recombinant fusion protein having the amino acid sequence represented by SEQ ID NO 4 as Applicant now proposes to claim. In particular, as referenced in the Office actions Papers No. 13 and 21, Wang shows the reactivity in Table 7 of peptides termed VIIIE, VIIID, VIIIC, and VIIIB which all contain the HCV core amino acid sequence 21-40.

20 The arguments that Wang, in listing the advantages of using synthetic antigens, teaches away from using recombinant antigens are not found persuasive because, while it is true that certain advantages are associated with using synthetic antigens, one of ordinary skill in the art at the time the invention was made would have recognized that there are advantages as well to using recombinant antigens as previously discussed, and if one were willing to forego the advantages of synthetics in favor of the known advantages of recombinants, then one would have been adequately motivated to select recombinant antigens. Wang herself realized that recombinant antigens may be substituted for synthetic antigens: Wang, col. 25, lines 29-42.

25 In addition, arguments referring to Wang's results as compared to C100 and the instant antigen's results compared to C100 are not fully persuasive because it appears that the assays of Wang and the assays done using the instant antigen were not done using the same sera. (See Wang, col. 18, lines 9-15, with reference to the results presented in Table 7: "Each of these

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Art Unit 1802

-3-

peptides ... with a panel of HCV antibody positive sera, each selected as representative of a particular clinical population, ..."; the source of the sera used by Dr. Helting is not immediately clear.)

In re Bell as cited by Applicant is not believed to apply here since the entire nucleotide as well as the entire amino acid sequence of HCV was generally known at the time the invention was made (see Wang, paragraph bridging col. 3-4).

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication should be directed to Examiner Donna C. Wortman at telephone number (703) 308-1032.

Donna C. Wortman, Ph.D.
October 27, 1993

Esther Kepplinger
ESTHER L. KEPPLINGER
SUPERVISORY PATENT EXAMINER
GROUP ART UNIT 1802

***** APPLICATION INFORMATION DISPLAY *****

DETAIL

INFORMATION:

E260177

F616369

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ISSDT: 00/00/00

ABNDT: 00/00/00

APPL: ZEBEDEE

LOC: 1801 LOC DT: 11/04/93 BATNO: 000

CHG-LOC: ISSNO: 00

CHGTO-NAME: NO NAME FOUND

TOT ACT: 05 STATUS: 083 STADT: 11/01/93

RESP CD: FR.. START DT: 07/12/93 DUE DT: 10/12/93

EXMR NO/NAME: 69422/WORTMAN, DONNA

DOCKET DATE: 7/7 GAU: 1802 L&R CD: 01

ATTY DOCK NO: PHA0026 LOST: N LOST DT: 00/00/00

APPLN TYPE: 1 TYPE SM ENT: 0 UNMAT PET: N

CURR CL/SC: 435/005.000 FOR PRIOR CL: N

TITLE OF INVENTION: UNAVAIL FOR ACTION: N PP UNAVAIL: 0

NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND
VACCINES

END OF DISPLAY TO DISPLAY CONTENTS: PUSH TAB KEY TWICE, PUSH SEND

840-117

1802
#25
3294



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.

Serial No.: 07/616,369

Filed: November 21, 1990

For: NON-A, NON-B, HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHODS AND
VACCINES

Examiner: D. Wortman

) Attorney Docket

) PHA 0026P

) Group Art Unit: 1802

RECEIVED

PETITION UNDER 37 C.F.R. §1.17

FEB 01 1994

GROUP 1800

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

A three-month extension of time to respond to the Final Rejection mailed July 12, 1993 is respectfully requested. This Petition is requested in order to allow the applicants to file a Notice of Appeal, enclosed herewith.

There is submitted herewith the following:

1. Check No. 21520 in the amount of the required fee of \$840.00 for the three-month extension of time (a response to the Final Rejection was due on October 12, 1993);
2. Notice of Appeal, in duplicate; and
3. Check No. 21521 in the amount of \$270.00 for the fee for the Notice of Appeal.

The Commissioner is hereby authorized to charge payment of any additional fees or credit any overpayment to Deposit Account No. 23-0920. A duplicate copy of this paper is enclosed.

100 MG 01/31/94 07616369

1 117 840.00 CK

01/31/94 MG#100 07616369


419 270.00

Serial No. 07/616,369

-2-

Please note that the undersigned has moved his practice to the address below, while maintaining the Power of Attorney in this application. Please forward all further communications concerning this application to counsel at the address shown below.

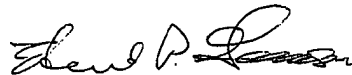
Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381

WELSH & KATZ, LTD.
Suite 1625
135 South La Salle Street
Chicago, Illinois 60603
312/781-9470

CERTIFICATE OF MAILING

I hereby certify that this Petition, in duplicate, together with the aforementioned documents and the required fees, is being deposited with the United States Postal Service as First Class Mail, postage prepaid, on January 11, 1994, addressed to Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231.



270-119

PHA-0026P
14829325

1802



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED

FEB 01 1994

GROUP 1800

Abon List

Applicant: Zebedee et al.

Serial No.: 07/616,369

Filed: November 21, 1990

For: NON-A, NON-B, HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC
METHODS AND VACCINES

Group Art Unit: 1802

Examiner: D. Wortman

Attorney

Docket No.: PHA-0026P

I hereby certify that this paper
is being deposited with the United States
Postal Service as first class mail in an
envelope addressed to: Commissioner of
Patents and Trademarks, Washington, D.C.
20231, on this date

Date: 1/11/94
Registration No. 29,381
Attorney for Applicant(s)

NOTICE OF APPEAL FROM THE PRIMARY EXAMINER TO THE BOARD OF APPEALS

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

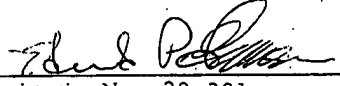
Sir:

Applicant hereby appeals to the Board of Appeals from the decision dated
7/12/93 of the Primary Examiner finally rejecting claims 35 and 39-46, inclusive

The item(s) checked below are appropriate:

1. ☒ (X) A Petition for Extension of Time to respond to the final rejection is filed herewith.
2. ☒ (X) Fee amount \$270.00.
- ☒ (X) Enclosed:
- ☐ () Not required (fee paid in prior appeal).
- ☒ (X) The Commissioner is hereby authorized to charge any additional fee which may be required, or credit any overpayment to Deposit Account No. 23-0920. Should no proper payment be enclosed, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 23-0920. (One additional copy of this Notice is enclosed herewith.)

Dated: January 11, 1994


Registration No. 29,381

Address to which Correspondence is to be sent:

WELSH & KATZ, LTD.
135 South LaSalle Street
Suite 1625
Chicago, Illinois 60603
(312) 781-9470

NOTAPL BOA/1092



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.

Serial No.: 07/616,369

Filed: November 21, 1990

For: NON-A, NON-B, HEPTATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHODS AND
VACCINES

Examiner: D. Wortman

) Attorney Docket
) PHA 0026P
) (2673/59325)
)
) Group Art Unit 1800

PETITION UNDER 37 C.F.R. §1.17

Box FWC
Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

RECEIVED
JUL 27 1994
GROUP 1800

Sir:

A four-month extension of time to file the Appellants' Brief on Appeal is respectfully requested. The Brief was due March 11, 1994. This extension of time is requested to allow the appellants to file a continuation application under 37 C.F.R. 1.62 enclosed herewith.

Enclosed is Check No. 2376/ in the amount of the required fee of \$1,320.00 for the four-month extension of time.

The Commissioner is hereby authorized to charge payment of any additional fees under 37 C.F.R. §1.17 to cover the cost of the extension or credit any overpayment to Deposit Account No. 23-0920. A duplicate copy of this paper is enclosed.

Respectfully submitted,

By Edward P. Gamson
Edward P. Gamson, Reg. No. 29,381

WELSH & KATZ, LTD.
135 South La Salle Street
Chicago, Illinois 60603
312/781-9470

1,320. - 118 7/12

9/13

FWC sent to A.

Serial No. 07/616,369

-2-

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that this Petition, in duplicate, together with the aforementioned documents and the required fees, is being deposited as Express Mail No. TB598475460 on July 8, 1994, addressed to Box FWC, Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Robert Smith

PATENT APPLICATION FEE DETERMINATION RECORD

For Fees Effective Nov. 5, 1990

Application or Docket Number

616,369

CLAIMS AS FILED - PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)
BASIC FEE		
TOTAL CLAIMS	74 minus 20 =	54
INDEPENDENT CLAIMS	7 minus 3 =	4
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY

RATE	FEE
	\$ 315.00
x \$10 =	
x 30 =	
+ 100 =	
TOTAL	

OR OTHER THAN SMALL ENTITY

RATE	FEE
	\$ 630.00
x \$20 =	1080
x 60 =	240
+ 200 =	300
TOTAL	2150

CLAIMS AS AMENDED - PART II

AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT (Column 1)	HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)
Total	*	Minus **	=
Independent	*	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM			

SMALL ENTITY

RATE	ADDITIONAL FEE
x \$10 =	
x 30 =	
+ 100 =	
TOTAL ADDIT. FEE	

OR OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE
x \$20 =	
x 60 =	
+ 200 =	
TOTAL ADDIT. FEE	

AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT (Column 1)	HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)
Total	* 12	Minus ** 24	=
Independent	* 1	Minus *** 7	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM			

SMALL ENTITY

RATE	ADDITIONAL FEE
x \$10 =	
x 30 =	
+ 100 =	
TOTAL ADDIT. FEE	

OR OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE
x \$20 =	
x 60 =	
+ 200 =	
TOTAL ADDIT. FEE	

AMENDMENT C	CLAIMS REMAINING AFTER AMENDMENT (Column 1)	HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)
Total	*	Minus **	=
Independent	*	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM			

SMALL ENTITY

RATE	ADDITIONAL FEE
x \$10 =	
x 30 =	
+ 100 =	
TOTAL ADDIT. FEE	

OR OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE
x \$20 =	
x 60 =	
+ 200 =	
TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PTO/SB/06 (11-90)

For Fees Effective Nov. 5, 1990

Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PALM III APPLICATION FILE DATA CODING SHEET

U.S. DEPARTMENT OF COMMERCE-PATENT & TM OFFICE

12/25/90

DATE

6-20-91

FORM 616-369

TYPE

FILING DATE

SPECIAL HANDLING

GROUP CLASS

SHEETS OF DRAWINGS

ASGT

TOTAL CLAIMS

INDEPENDENT CLAIMS

SMALL ENTITY?

FILING FEE RECEIVED

SECURITY FOREIGN CASE? LICENSE?

07

1

11/21/90

184

435

11

53

7

7

2278

2278

2278

FORMAT NO. 3

ATTORNEY DOCKET NUMBER (12 spaces)

Att. s Reg. No.

FORMAT NO. 4

Applicant's Name & Address

FORMAT NO. 5

Title of Invention

FORMAT NO. 6

Correspondence Address

FORMAT NO. 8

CONTINUITY CODE

PARENT APPLICATION SERIAL NUMBER

PARENT FILING DATE

STATUS CODE

PARENT PATENT NUMBER

83

7573643

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2

RECORD

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☐ MORE ON SUPPLEMENTAL CODING SHEET

FORMAT NO. 9

COUNTRY CODE

PCT/FOREIGN APPLICATION SERIAL NUMBER

Month

Day

Year

FILING DATE

RECORD

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☐ MORE ON SUPPLEMENTAL CODING SHEET

☐ APPLICATION PAPERS

☒ YES
☐ NO

REIGN COUNTRY CLAIMED?

**MULTIPLE DEPENDENT CLAIM
FEE CALCULATION SHEET
(FOR USE WITH FORM PTO-875)**

SERIAL NO.

616,369

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2	1					
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TOTAL IND.						
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TOTAL CLAIMS						

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51		1				
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TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

PATENT APPLICATION SERIAL NO. 08/272271

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

010 TL 07/20/94 08272271

1 101 710.00 CK

PTO-1556
(5/87)



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

TB598475460US

July 8, 1994

"Express Mail" mailing number

Date of Deposit

I hereby certify that this application is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Box FWC, Washington, D.C. 20231.

Robert Smith

Typed or printed name of person mailing application

Signature of person mailing application

Anticipated Classification of this Application:

Class _____ Subclass _____

Prior Application:

Examiner D. Wortman

Art Unit 1802

COMMISSIONER OF PATENTS AND TRADEMARKS

Box FWC

Washington, D.C. 20231

Sir:

FILING UNDER 37 CFR 1.62 WITH
ABANDONMENT OF THE PENDING PRIOR APPLICATION

This is a Request for filing a ☐ continuation-in-part, ☒ continuation, ☐ divisional application under 37 CFR 1.62 of prior application Serial No. 07/616,369, filed on November 21, 1990, entitled NON-A, NON-B HEPATITIS VIRUS ANTIGEN, DIAGNOSTIC METHODS AND VACCINES by the following named inventor(s).

FULL NAME OF INVENTOR	FAMILY NAME Zebedee 1-00	FIRST GIVEN NAME Suzanne	SECOND GIVEN NAME --
RESIDENCE & CITIZENSHIP	CITY San Diego	STATE OR FOREIGN COUNTRY California CA	COUNTRY OF CITIZENSHIP U.S.A.
POST OFFICE ADDRESS	POST OFFICE ADDRESS 7544 Charmant Drive	CITY San Diego	STATE & ZIP CODE/COUNTRY California 92122
FULL NAME OF INVENTOR	FAMILY NAME Inchausepe 2-00	FIRST GIVEN NAME Genevieve	SECOND GIVEN NAME --
RESIDENCE & CITIZENSHIP	CITY New York	STATE OR FOREIGN COUNTRY New York NY	COUNTRY OF CITIZENSHIP France
POST OFFICE ADDRESS	POST OFFICE ADDRESS 504 East 63rd Street	CITY New York	STATE & ZIP CODE/COUNTRY New York 20021
FULL NAME OF INVENTOR	FAMILY NAME Nasoff 3-00	FIRST GIVEN NAME Marc	SECOND GIVEN NAME S.
RESIDENCE & CITIZENSHIP	CITY San Diego	STATE OR FOREIGN COUNTRY California CA	COUNTRY OF CITIZENSHIP U.S.A.
POST OFFICE ADDRESS	POST OFFICE ADDRESS 11734 Mira Lago Way	CITY San Diego	STATE & ZIP CODE/COUNTRY California 92131

continued ...

Page 1 of 3

08/272271

#27/C

8/23/94

FIVE sent to G 1000

continued from page 1

FULL NAME OF INVENTOR	FAMILY NAME Prince	FIRST GIVEN NAME Alfred	SECOND GIVEN NAME M.
RESIDENCE & CITIZENSHIP	CITY New York	STATE OR FOREIGN COUNTRY New York NY	COUNTRY OF CITIZENSHIP U.S.A.
POST OFFICE ADDRESS	POST OFFICE ADDRESS Pound Ridge 154 Stone Gill Road/	CITY New York	STATE & ZIP CODE/COUNTRY New York 10576
FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

The above-identified prior application in which no payment in the issue fee, abandonment of, or termination of proceedings has occurred, is hereby expressly abandoned as of the filing date of this new application. Please use all the contents of the prior application file wrapper, including the drawings, as the basic papers for the new application. (Note: 37 CFR 1.60 may be used for applications where the prior application is not to be abandoned.)

1. ☒ Enter the amendment previously filed on October 12, 1993 under 37 CFR 1.116 but unentered, in the prior application.
2. ☐ A preliminary amendment is enclosed.

The filing fee is calculated on the basis of the claims existing in the prior application as amended at 1 and 2, above.

CLAIMS	Claim Type	Number Filed	Number Extra	Rate	Calculations
	Total Claims	9 - 20 =	-0-	x \$ 22.00	\$ --
	Independent Claims	1 - 3 =	-0-	x \$ 74.00	--
	Multiple Dependent Claim(s) (if applicable)			+ \$230.00	--
				Basic Fee	+ 710.00
				Total of Above Calculations =	\$710.00
	Reduction by 1/2 for filing by small entity (Note 37 CFR 1.9, 1.27, 1.28), if applicable, affidavit must be filed also.				- --
				Total National Fee	\$ 710.00

3. ☒ The Commissioner is hereby authorized to charge fees under 37 CFR 1.16 and 1.17 which may be required, or credit any overpayment to Deposit Account No. 23-0920.
4. ☒ A check in the amount of \$ 710.00 is enclosed.
5. ☐ A new oath or declaration is included since this application is a continuation-in-part which discloses and claims additional matter.
6. ☒ Amend the specification by inserting before the first line the sentence:

21 - This application is a ☐ continuation-in-part, ☒ continuation, ☐ division, of application
Serial No. 07/616,369, filed November 21, 1990, -

7. ☐ A verified statement claiming small entity status is enclosed (not necessary if statement was filed in the prior application).
8. ☐ Priority of application Serial No. _____ filed on _____ in _____
is claimed under 35 U.S.C. 119.
9. ☒ The prior application is assigned of record to Pharmacia Genetic Engineering, Inc. and
The New York Blood Center
10. ☒ The power of attorney in the prior application is to: Edward P. Gamson, Reg. No. 29,381

11. ☐ The small entity statement was filed in the parent application Serial No. _____ on _____ and this status is still proper and its benefit under 37 CFR 1.28(a) is hereby claimed.

12. ☒ Also enclosed:

Petition, in duplicate, for a four-month extension of time in
Serial No. 07/616,369

Address all future communications to: (May only be completed by applicant, or attorney or agent of record.)

WELSH & KATZ, LTD.
Suite 1625
135 South La Salle Street
Chicago, Illinois 60603
Telephone: 312/781-9470

It is understood that secrecy under 35 U.S.C. 122 is hereby waived to the extent that if information or access is available to any one of the applications in the file wrapper of a 37 CFR 1.62 application, be it either this application or a prior application in the same file wrapper, the Patent and Trademark Office may provide similar information or access to all the other applications in the same file wrapper.

Date: July 8, 1994



Attorney's Signature

(1) Name and Reg. No. Edward P. Gamson, 29,381



GP182

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 08/272,271) Attorney Docket
Filed: July 8, 1994) PHA-0026P CON I
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: Not yet assigned)

WORTMAN

#28
7/23/94
11/15/94

INFORMATION DISCLOSURE STATEMENT

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

RECEIVED
OCT 14 1994
GROUP 1800

Sir:

Pursuant to 37 C.F.R. §1.97, a list of documents is disclosed on the attached forms PTO-1449 that may be material to the examination of this application. The subject application is a continuation application of Serial No. 07/616,369, filed November 21, 1990 that was one of three related applications referred to herein as the "grandparent", "parent", and "child" applications. The serial numbers and filing dates of those applications are 07/573,643, filed on August 25, 1990 (the grandparent application), 07/616,369 filed on November 21, 1990 (the parent application and a C-I-P of the grandparent application), and 07/748,564 filed on August 21, 1991 (the child application and a C-I-P application of the parent application).

Listed documents A and D-N on the attached form PTO-1449 are cited and discussed in all three applications.

Listed documents AA-AG are included on the list as general background art related to the work of some of the present inventors on non-A/non-B hepatitis viruses.

Listed documents B, C and AH were cited in the International Search Report for PCT Application PCT/US91/06037,

which application corresponds to the child application. A copy of that International Search Report is enclosed for the Examiner's convenience.

Five papers of possible interest here, at least four of which were published after the filings of both Wang and the present application, have come to counsel's attention and are noted here to complete the record and underscore that which has already been discussed. The first paper published is by Wang and her co-workers [Hosein et al., Proc. Natl. Acad. Sci. USA, 88:3647-3651 (May 1991)]. The second is by two of the present inventors and their co-workers [Sugitani et al., Lancet, 339:1018-1019 (April 1992)]. The third, by inventors herein [Nasoff et al., Proc. Natl. Acad. Sci. USA, 88:5462-66 (1991)] was published prior to the Wang paper. The fourth paper is Okamoto et al., Japan. J. Exp. Med., 60:222-233 (1990), whereas the fifth is Okamoto et al., Hepatology, 15:180-186 (1992).

The first paper (BA) discusses assays run using chemically synthesized peptides. An unidentified capsid (core) peptide "selected from a region covered by amino acids 1-120" was used as the single antigen in EIA I, peptides from two non-structural proteins were used in EIA II and all three peptides were used in EIA III. These three formats are thus similar to Formats A, B and C of the Wang patent.

Although there is not an exact identity of data (presumed to be due to the typographical errors because of the complete identity of the remaining data), it is believed that the data of Table 1 of this paper for donor 1 are the same as those of Table 8 of the Wang patent for panel 1. Similarly, the results of the second paragraph on the left side of page 3649 for Japanese dialysis patients can be obtained by ready calculation from the data of the Wang patent Table 9. That being the case,

the peptides of EIA II correspond to those of Format A of the Wang patent, whereas the EIA III peptides are those of Format C of the patent that used peptides IIH, V and VIIIE. Inasmuch as EIA III is said in the paper to contain all three peptides of EIA I and EIA II, the peptide of EIA I must have been peptide VIIIE of the patent.

This paper discusses the added sensitivity of anti-HCV antibody detection when a capsid synthetic peptide is added to peptides from non-structural proteins, including earlier detection of seroconversion as compared to the C-100 antigen-based assays. Missing, however, are data for the capsid synthetic peptide alone; i.e., peptide VIIIE.

The second paper (BB) compares various assays that include a Wang group kit (UBI-HCV, reference 5) an assay of the present invention (Capsid) and C100 kit used for comparison herein (C100-3). The data of the table show that an assay of the present invention based on a recombinant capsid corresponding to residues 1-120 was equally sensitive to the UBI-HCV kit containing three peptides and a second generation kit from Abbott (Abbott-II) that contains two non-structural antigens and a capsid antigen. All three identified 13/19 or 68 percent of the PCR-positive sera.

Thus, another unexpected result is found here. An assay of the claims based on a single recombinant whole protein (Fig. 1., residues 1-120) was as sensitive as an assay based on a mixture of three chemically synthesized peptides from three different proteins.

Enclosed paper three (BC) describes the CAP-N antigen used in the present application. Although the nomenclature is different, it is apparent that the capsid antigen designated CAP-A of BB is the CAP-N antigen of the present application.

Document BD is an apparent follow-up to the Okamoto et al. paper of record herein that is cited twice in the paragraph bridging pages 1 and 2 of the present application. This paper deals with the use of a 36-mer synthetic peptide that contains residues 39-74 of the HCV capsid as an antigen in an assay for anti-HCV antibodies.

The first page of the article indicates that it was received for publication on June 13, 1993. A computer-assisted search in the MEDLINE data base of DIALOG Information Services, Inc., indicates that Document BD was published in August of 1990. The mailing and receipt dates of this article are unknown, but are being sought from counsel's Japanese associates and will be provided to the Examiner on receipt.

As is seen from the Summary, the anti-synthetic peptide assay (anti-CP9) and the commercial anti-HCV assay overlapped with positive results in 54 percent of 324 cases of acute or chronic NANB liver disease, with 18 percent of the sera being positive only in the anti-CP9 assay and another 15 percent of the sera being positive in the anti-HCV assay and negative in the anti-CP9 assay, leaving another 13 percent undetected in either assay.

Document BE published in 1992 is an apparent follow-up to Document BD. Here, another synthetic peptide was used in the assays. That peptide was designated CP10, and includes 19 residues covering amino acid residue positions 5-23 of Fig. 1. It is noted that this paper used the two peptides separately and summed the results obtained from separate assays rather than linking the peptides or using a mixture of both in the assays.

In accordance with 37 C.F.R. §1.98(2)(d), a copy of each of the listed documents was included with the Information

Disclosure Statement filed with the grandparent application on April 10, 1992 and can be found in that application file.

Pursuant to 37 C.F.R. 1.98(d), it is understood that only a list of art is required inasmuch as the art has been provided and discussed previously.

No inferences should be drawn that the attached list represent a comprehensive investigation, or that any material disclosed is equivalent to the subject invention. In addition, none of the documents that have publication dates prior to the priority date of the above application anticipate the invention in this application.

The cited documents disclose numerous specific features. There has been no attempt to list each and every feature disclosed by each document. The Examiner is requested to review the documents and determine the extent of the materiality of the document disclosures with respect to the present invention.

The discussion of any art and the citation of any document herein is not to be construed as an admission that the art or document disclosure is necessarily within the invention field of endeavor, that the art or document disclosure is necessarily prior in time to a particular date which may be relevant to the instant patent application, and/or that the art or document disclosure is otherwise necessarily prior art as defined by the patent law with respect to the instant invention and application.


Also, there is reserved the right to later set forth how the instant invention is distinguished over the disclosure of any document or other art, including the disclosures of the art and documents recited herein, that may be cited by the Examiner in rejecting a claim in the instant patent application.

Serial No. 08/272,271

-6-

The recitation herein of the art and documents is not to be construed as an assertion that more pertinent art could not possibly be in existence.

Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381

Enclosures:

Two (2) Forms PTO-1449
Copy of the International Search Report for
PCT Application PCT/US91/06037, which
corresponds to U.S. Patent Application
Serial No. 07/748,564

WELSH & KATZ, LTD.
135 South La Salle Street
Chicago, Illinois 60603
312/781-9470

CERTIFICATE OF MAILING

I hereby certify that this Information Disclosure Statement, together with the stated enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on October 6, 1994.



Serial No.
08/272,271

Sheet 1 of 3

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

Filing Date
July 8, 1994

Group 88
Not yet assigned

U.S. PATENT DOCUMENTS

[illegible]

RECEIVED
OCT 14 1994
GROUP 1800

FOREIGN PATENT DOCUMENTS

[illegible]

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

D	Choo-et-al, <u>Science</u> , <u>244</u> , 359-362 (1989)
E	Okamoto-et-al, <u>Japan J. Exp. Med.</u> , <u>60</u> , 163-177 (1990)
F	Miller-et-al., <u>PNAS</u> <u>87</u> , 2057-2064 (1990)
G	Kuo-et-et, <u>Science</u> <u>244</u> , 362-364 (1989)
H	Alter et al. <u>NEJM</u> <u>321</u> , 1538-39 (1989)

Examiner [Signature] Date Considered [Signature]

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.



Sheet 2 of 3

(Rev. 5/92) Comparable to Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	App. Docket No. 0026P CON I	Serial No. 08/272,271
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)		Applicant Zebedee et al.	
		Filing Date July 8, 1994	Group 1802 Not yet assigned
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)			
I	Atter et al., NEJM, 321, 1494-1500 (1988)		
J	Wolner et al., Lancet, 332, 1-3 (1990)		
K	McFarlane et al., Lancet, 332, 754-757 (1990)		
L	Gray et al., Lancet, 332, 609-610 (1990)		
M	Houghton et al., Int. K. Prot. Reg., 16, 311-320 (1980)		
O	Choo et al., PHAS, 88-2454-2455 (1991)		
P	Takamizawa et al., J. Virol., 62, 1105-1113 (1994)		
Q	Kato et al., PHAS, 87, 9524-9528 (1990)		
R	Takeuchi et al., NUCLEIC ACIDS RES., 18, 4626 (1990)		
S	Qgata et al., PHAS, 88, 3392-3396 (1994)		
T	Han et al., PHAS, 88, 1111-1113 (1991)		
U	Meyen et al., Virol., 171, 555-567 (1989)		
V	Collett et al., Virol., 165, 191-199 (1988)		
W	Brinton et al., Virol., 162, 290-299 (1988)		
X	Ischeuspe et al., PHAS, 88, 10292-10296 (1994)		
Y	Werner et al., Virol., 188, 842-848 (1991)		
Z	Hahn et al., Virol., 168, 167-180 (1988)		
AA	Prince et al., Lancet, 2, 241 (1974)		
AB	Prince et al., "POSTTRANSFUSION Viral Hepatitis Caused by an Agent or Agents Other Than Hepatitis B Virus or Hepatitis A Virus: Impact On Efficiency of Present Screening Methods." in Transmissible Disease & Blood Transfusion, Ilbor et al., eds., Grune & Stratton, Inc., pp. 129-140 (1975)		
AC	Prince et al., "Non-A/Non-B Hepatitis: Identification of a virus-specific antigen and antibody. A preliminary report." in Viral Hepatitis, Vyas et al., eds., Franklin Institute Press, Philadelphia, Pa. pp. 633-640 (1978).		
AD	Prince et al., "Non-A/Non-B Hepatitis: Reproduction of disease in chimpanzees and identification of virus specific antigen and antibody." in Transplantation and Clinical Immunology, Volume X, Touraine et al., eds., Excerpta Medica, Amsterdam, pp. 8-17 (1979).		
AE	Bainroy et al., Lancet, May-22, 1982.		
Examiner	Date Considered		
*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.			

RECEIVED
OCT 14 1994
GROUP 1800all documents
received



Sheet 3 of 3

(Rev. 5/92)
Comparable to
Form PTO-1449

U.S. Department of Commerce
Patent and Trademark Office

Serial No.
08/272,271

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

Filing Date
July 8, 1994

Group
Not yet assigned

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

AF Prince et al., "Use of liver cell cultures in studies on the replication of hepadna and non-A, non-B viruses" in *Viral Hepatitis and Liver Disease*, Grune & Stratton, pp. 459-464 (1984).

AG Brotman et al., *J. Infect. Diseases*, 151(4):618 (1985).

AH Takeuchi et al., *Gene*, 91:287 (1990).

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OCT 14 1994
GROUP 1800

Examiner

Date Considered

3/10/95

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.



Sheet 1 of 1

(Rev. 5/92)
Comparable to
Form PTO-1449U.S. Department of Commerce
Patent and Trademark OfficeAtty. Docket No.
PDA-0026P CON ISerial No.
08/272,271INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)Applicant
Zebedee et al.Filing Date
July 8, 1994Group
Not yet assigned

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

BA ~~Hosein et al., Proc. Natl. Acad. Sci. USA, 88:3647-3651 (May 1991)~~ *of record*

BB ~~Sugitani et al., Lancet, 339:1018-1019 (April 1992)~~ *of record*

BC ~~Nasoff et al., Proc. Natl. Acad. Sci. USA, 88:5462-66 (1991)~~ *of record*

BD ~~Okamoto et al., Japan. J. Exp. Med., 60:222-233 (1990)~~ *of record*

BE ~~Okamoto et al., Hepatology, 15:180-186 (1992)~~ *of record*

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OCT 14 1994
GROUP 1800

Examiner

Date Considered

*Examiner:

Initial if citation considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PATENT COOPERATION TREATY

New York Blood Center
Office of Patents & Licenses
310 East 67th St.
New York, N.Y.
10021

EP 2/1492
FEB 8 1992
UNITED STATES
INTERNATIONAL SEARCHING AUTHORITY
NOTIFICATION OF TRANSMITTAL OF
DRESSLER GOLDSMITH, JEFFREY
SUTKEN & MILHAM, THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION
Issued pursuant to PCT Rule 44.1

*for 2/4/92
MSP*

Inscribe NAME and ADDRESS of the AGENT and if there
is no agent, of the APPLICANT

DATE OF MAILING by the International Searching Authority **24 JAN 1992**

APPLICANT'S OR AGENT'S FILE REFERENCE
PHA 0029

IDENTIFICATION OF THE INTERNATIONAL APPLICATION

International Application No. PCT/US91/06037	International Filing Date 23 August 1991
Applicant (Name) New York Blood Center	

NOTIFICATION

The applicant is hereby notified that, in regard to the above-identified international application, this International Searching Authority transmits herewith:

1. ☒ the international search report.

THE ATTENTION OF THE APPLICANT IS DRAWN TO THE TIME LIMIT FOR AMENDING BEFORE THE INTERNATIONAL BUREAU ACCORDING TO ARTICLE 19(1) AND RULE 46.1 WHICH RUNS FROM THE DATE OF MAILING OF THE INTERNATIONAL SEARCH REPORT

2. ☐ the declaration to the effect that no international search report will be established.

THE ATTENTION OF THE APPLICANT IS DRAWN TO THE TIME LIMIT FOR COMPLYING WITH THE REQUIREMENTS OF ARTICLE 22(2).

☐ Applicant is further notified that, the protest against payment of an additional fee under Rule 40.2(c) together with the decision thereon has been transmitted to the International Bureau together with the request to forward the texts of both the protest and the decision thereon to designated Offices.

THE UNITED STATES INTERNATIONAL SEARCHING AUTHORITY

Address only:
Commissioner of Patents and Trademarks
Box PCT
Washington, D. C. 20231

Attn: ISA/US

Authorized Officer

Donna Wortman

James W. Mansel for

PATENT COOPERATION TREATY INTERNATIONAL SEARCH REPORT

IDENTIFICATION OF INTERNATIONAL APPLICATION		Applicant's or Agent's File Reference PHA 0029
International Application No. PCT/US91/06037	International Filing Date 23 August 1991	
Receiving Office RO/US	Priority Date Claimed 25 August 1990	
Applicant New York Blood Center		
I. <input type="checkbox"/> CERTAIN CLAIMS WERE FOUND UNSEARCHABLE: (Observations on supplemental sheet (2)) II. <input type="checkbox"/> UNITY OF INVENTION IS LACKING: (Observations on supplemental sheet (2))		
III. TITLE, ABSTRACT AND FIGURE OF DRAWING		
1. The following indicated items are approved as submitted by the applicant: 3 <input checked="" type="checkbox"/> Title. <input checked="" type="checkbox"/> Abstract.		
2. The texts established by this International Searching Authority of the following indicated items are set forth below: <input type="checkbox"/> Title. <input type="checkbox"/> Abstract.		
<div style="text-align: center; font-size: 2em; opacity: 0.5;"> (This area is for the text of the abstract and the figure of the drawing.) </div>		
Text of the abstract continued on supplemental sheet 3. a. <input type="checkbox"/> The definitive contents of the abstract are established by this International Searching Authority as proposed in form PCT/ISA/204 previously sent to the applicant. b. <input type="checkbox"/> This report is incomplete as far as the abstract is concerned as the time limit for comments by the applicant on the draft prepared by this International Searching Authority has not expired.		
4. Figure to be published with the abstract Figure No. <u>1</u> <input type="checkbox"/> None of the figures. <input checked="" type="checkbox"/> as suggested by the applicant <input type="checkbox"/> because the applicant failed to suggest a figure <input type="checkbox"/> because this figure better characterizes the invention		

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/06037

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC U.S. CL.: 536/27; 530/350, 387; 435/5; 424/89 IPC(5): C07H 15/12; C07K 3/00; C12Q 1/70; A61K 39/12		
II. FIELDS SEARCHED Minimum Documentation Searched?		
Classification System	Classification Symbols	
U.S.	536/27; 530/350, 387; 435/5; 424/89	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁷		
STIC Sequence Search APS		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁸		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	Gene, Volume 91, issued 1990, K. Takeuchi et al., "Hepatitis C viral cDNA isolated from a healthy carrier donor implicated in post-transfusion non-A, non-B hepatitis," pages 287-291, see entire document.	1,3-6
X Y	EP, A, 0,318,216 (Houghton et al.) 31 May 1989, see figures and claims.	16 3-15,17-45
X Y, P	EP, A, 0,388,232 (Houghton et al.) 19 September 1990, see figures and claims.	16 1-15,17-45
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 07 January 1992		Date of Mailing of this International Search Report 24 JAN 1992
International Searching Authority ISA/US		Signature of Authorized Officer Donna C. Wortman

International Application No. PCT/US91/06037

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . . because they relate to subject matter¹² not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out¹³, specifically:

3. ☐ Claim numbers . . . because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

See attached sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application. Telephone practice

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

#25
AU 1802 3-1348

PAGE: 1

RAW SEQUENCE LISTING
PATENT APPLICATION US/08/272,271

DATE: 10/07/94
TIME: 07:04:04

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This Raw Listing contains the General
Information Section and up to the first 5 pages.

Wentman

SEQUENCE LISTING

ENTERED

(1) General Information:

(i) APPLICANT: Zebedee, Suzanne
Inchauspe, Genevieve
Nasoff, Marc
Prince, Alfred

(ii) TITLE OF INVENTION: NON-A, NON-B HEPATITIS VIRUS ANTIGEN,
DIAGNOSTIC METHODS AND VACCINES

(iii) NUMBER OF SEQUENCES: 45

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: DRESSLER, GOLDSMITH, SHORE, SUTKER &
MILNAMOW, LTD
(B) STREET: 11300 Sorrento Valley Road
(C) CITY: San Diego
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 92121

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US/08/272,271
(B) FILING DATE:
(C) CLASSIFICATION:

(v) PRIOR APPLICATION DATA;

(A) APPLICATION NUMBER: US 07/616,369
(B) FILING DATE: 21-NOV-1990
(A) APPLICATION NUMBER: US 07/573,643
(B) FILING DATE: 25-AUG-1990
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Bingham, Douglas A.
(B) REGISTRATION NUMBER: 32,457
(C) REFERENCE/DOCKET NUMBER: PHA0026P

RAW SEQUENCE LISTING
PATENT APPLICATION US/08/272,271DATE: 10/07/94
TIME: 07:04:15

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47 (ix) TELECOMMUNICATION INFORMATION:
48 (A) TELEPHONE: 619-546-1555
49 (B) TELEFAX: 619-546-1380
50
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52 (2) INFORMATION FOR SEQ ID NO:1:
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54 (i) SEQUENCE CHARACTERISTICS:
55 (A) LENGTH: 978 base pairs
56 (B) TYPE: nucleic acid
57 (C) STRANDEDNESS: single
58 (D) TOPOLOGY: linear
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60 (ii) MOLECULE TYPE: DNA (genomic)
61
62 (iii) HYPOTHETICAL: NO
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64 (iv) ANTI-SENSE: NO
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68 (A) NAME/KEY: CDS
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76 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
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RAW SEQUENCE LISTING PATENT APPLICATION US/08/272,271

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TIME: 07:04:45

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167 (B) TYPE: nucleic acid
168 (C) STRANDEDNESS: single
169 (D) TOPOLOGY: linear
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171 (ii) MOLECULE TYPE: DNA (genomic)
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175 (iv) ANTI-SENSE: NO
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RAW SEQUENCE LISTING PATENT APPLICATION US/08/272,271

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228		
229	GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC	576
230	Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr	
231	180 185 190	
232		
233	TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC	624
234	Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala	
235	195 200 205	
236		
237	ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG ATC GAA GGT	672
238	Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Ile Glu Gly	
239	210 215 220	
240		
241	CGT GGG ATC CCC AAT TCG AGC TCG GTA CCC ATG AGC ACG ATT CCC AAA	720
242	Arg Gly Ile Pro Asn Ser Ser Ser Val Pro Met Ser Thr Ile Pro Lys	
243	225 230 235 240	
244		
245	CCT CAA AGA AAA ACC AAA CGT AAC ACC AAC CGT CGC CCA CAG GAC GTC	768
246	Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp Val	
247	245 250 255	
248		
249	AAG TTC CCG GGT GGC GGT CAG ATC GTT GGT GGA GTT TAC TTG TTG CCG	816
250	Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu Pro	
251	260 265 270	
252		
253	CGC AGG GGC CCT AGA TTG GGT GTG CGC GCG ACG AGG AAG ACT TCC GAG	864
254	Arg Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser Glu	
255	275 280 285	
256		
257	CGG TCG CAA CCT CGA GGT AGA CGT CAG CCT ATC CCC AAG GCA CGT CGG	912
258	Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg Arg	

PAGE: 6

RAW SEQUENCE LISTING
PATENT APPLICATION US/08/272,271

DATE: 10/07/94
TIME: 07:05:15

INPUT SET: S1342.raw

***** PREVIOUSLY ERRORED SEQUENCES - EDITED *****

912 (2) INFORMATION FOR SEQ ID NO:21:
913
914 (i) SEQUENCE CHARACTERISTICS:
915 (A) LENGTH: 18 base pairs
916 (B) TYPE: nucleic acid
917 (C) STRANDEDNESS: single
918 (D) TOPOLOGY: linear
919
920 (ii) MOLECULE TYPE: DNA (genomic)
921
922 (iii) HYPOTHETICAL: NO
923
924 (iv) ANTI-SENSE: YES
925
926
927
928 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:
929
930 AGATAGAGAA AGAGCAAC
931

18

PAGE: 1

SEQUENCE VERIFICATION REPORT
PATENT APPLICATION US/08/272,271

DATE: 10/07/94
TIME: 07:05:24

INPUT SET: S1342.raw

Line	Error	Original Text
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08/272271


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
---------------	-------------	----------------------	---------------------

08/272,271 07/08/94 ZEBEDEE

S

WORTMAN EXAMINER

18N1/0321

 WELSH AND KATZ LTD
135 SOUTH LA SALLE STREET
SUITE 1625
CHICAGO IL 60603

ART UNIT PAPER NUMBER

1802

30

DATE MAILED: 03/21/95

 This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final

 A shortened statutory period for response to this action is set to expire 3 month(s), 28 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133
Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474.. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION1. ☒ Claims 35, 39-46 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-34, 36-38, 47-53 have been cancelled.3. ☐ Claims _____ are allowed.4. ☒ Claims 35, 39-46 are rejected.5. ☐ Claims _____ are objected to.6. ☐ Claims _____ are subject to restriction or election requirement.7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.8. ☐ Formal drawings are required in response to this Office action.9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.14. ☐ Other**EXAMINER'S ACTION**

Serial Number: 08/272271

-2-

Art Unit: 1802

Claims 36-38 were cancelled and Claim 35 was amended by preliminary amendment. Claims 35 and 39-46 are pending and under examination at this time.

Claims 39-46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 is indefinite because it recites "said recombinant NANBV structural protein" without clear antecedent in Claim 35 from which it depends. Claim 35 recites a "recombinant NANBV fusion protein."

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the

Serial Number: 08/272271

-3-

Art Unit: 1802

time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 35 and 38-46 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent 5,106,726 to Wang in view of Kuo et al., both previously of record, and further in view of Smith et al. (Genes 67:31-40, 1988, cited on PTO 892, attached). Wang teaches assaying sera for antibodies against HCV (NANBV) using solid phase coated with peptides that include the HCV core amino acid residue sequences as instantly claimed (see Wang, Example 14 and Table 7, especially peptide VIIIE) but exemplifies synthetic peptides rather than the particular recombinant fusion protein as instantly claimed. Wang additionally teaches that recombinant proteins can also be used (col. 25, lines 29-42). Kuo teaches production of an HCV:SOD recombinant fusion protein for use in immunoassays. Neither Wang nor Kuo teaches producing and using a HCV:GST recombinant fusion protein. Smith et al. teach a vector which results in GST fusion proteins and the advantages of the GST system, e.g., ease of product purification. It would have been obvious to one of ordinary skill in the art to

Serial Number: 08/272271

-4-

Art Unit: 1802

produce the HCV core antigen peptide of Wang as a recombinant fusion protein as taught by Kuo in order to gain the advantages of producing peptides by recombinant means, e.g., to obtain a stable, plentiful supply of peptides that are free of contamination with other HCV antigens and to use them in immunoassays with reasonable expectation for success because both Kuo and Wang successfully use HCV peptides to detect antibodies in sera. It would have been additionally obvious to one of ordinary skill in the art to make an HCV core antigen fusion protein with the substitution of the GST of Smith for the SOD of Kuo because Smith teaches the advantages of GST fusion proteins such as ease of purification (see, e.g., Smith, p. 32, paragraph bridging col.1-2) and, in the absence of unexpected results, to obtain an HCV core antigen:GST fusion protein which would function successfully in detecting HCV antibodies.

Claims 35 and 38-46 are rejected under 35 U.S.C. § 103 as being unpatentable over US patent 5,350,671 to Houghton et al. (cited on PTO 892, attached) in view of Smith et al. (cited above). Houghton teaches use of antigens from the C domain of HCV as well as recombinant HCV:SOD fusion proteins in HCV immunoassays, and the existence of important diagnostic epitopes located within the core or C domain of HCV (see, e.g., Fig. 63; Fig. 65; col. 50; the table of col. 83; col. 89, IV.B.13). Houghton differs from the instant invention in teaching fusion proteins of HCV amino acid sequences fused to SOD rather than to GST. Smith et al. teach production of GST fusion proteins and the advantages of the system, e.g., ease of product purification. It would have been obvious to one of ordinary skill in the art to make and use an HCV fusion protein as taught by Houghton with the

Serial Number: 08/272271

-5-

Art Unit: 1802

substitution of the GST of Smith for SOD because Smith teaches the advantages of GST fusion proteins such as ease of purification, and, in the absence of unexpected results, obtain an HCV:GST fusion protein which would function successfully to detect HCV antibodies because the HCV antigen would remain the same regardless of the portion of the fusion protein which is unrelated to HCV.


Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4065 and (703) 308-7939.

Any inquiry concerning this communication should be directed to Examiner Donna C. Wortman at telephone number (703) 308-1032.

Dew
Donna C. Wortman, Ph.D.
March 20, 1995

Toni R. Scheiner

TONI R. SCHEINER
SUPERVISORY PATENT EXAMINER
GROUP 1800

PTO 692		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NUMBER 08/272271		Art Unit 1802		Attachment to Paper Number 30	
NOTICE OF REFERENCES CITED									
				APPLICANT(S): Zobedee et al.					
U.S. PATENT DOCUMENTS									
*		DOCUMENT NUMBER	DATE	NAME(S)	CLASS	SUBCLASS	FILING DATE		
		5,350,871	9/1994	Houghton et al.	435	5	8/1993		
FOREIGN PATENT DOCUMENTS									
*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS	PERTINENT DRW SPEC	
*		OTHER REFERENCES (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)							
		Smith et al., Single-step purification of polypeptides expressed in <i>Escherichia coli</i> as fusions with glutathione S-transferase. Gene 87:31-40, 1988.							
EXAMINER 		DATE 3/20/95		* A COPY OF THIS REFERENCE IS NOT BEING FURNISHED WITH THIS OFFICE ACTION. (SEE MPEP SECTION 707.05(a).)					
PAGE 1 OF 1									

605 5470-117-1802

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant: Zebedee et al.)
Serial No.: 08/272,271) Attorney Docket
Filed: November 21, 1990) PHA-0026P CON I
(2673/61109)
For: NON-A, NON-B, HEPATITIS VIRUS)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: D. C. Wortman)

#31
11/14/95

PETITION UNDER 37 C.F.R. §1.17

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

SEP 19 1995

A three-month extension of time to respond to the
Office Action dated March 21, 1995, is respectfully requested.

There is submitted herewith the following:

1. Response; and

2. Check No. 029192 in the amount of \$500.00 and

Check No. 029193 in the amount of \$370.00 to total \$870.00 for
the three-month extension of time (a response to the Office
Action was due June 21, 1995).

No further fee or petition is believed necessary.

However, should any further fee be needed, please charge our
Deposit Account No. 23-0920 and deem this paper to be the
required petition. This paper is being filed in duplicate.

Respectfully submitted,

By Edward P. Gamson
Edward P. Gamson, Reg. No. 29,381

Enclosures

3-Month Petition for Extension and Fee
Response

Welsh & Katz, Ltd.
135 South LaSalle Street
Chicago, Illinois 60603-4302
Telephone: 312/781-9470

280 MM 10/05/95 08272271 1 117 500.00 CK

CERTIFICATE OF MAILING

I hereby certify that this Petition for three-month
extension of time, together with the stated enclosure(s) and
fee(s) are being deposited with the United States Postal Service
with sufficient postage as First Class Mail in an envelope
addressed to: Assistant Commissioner for Patents, Washington,
D.C. 20231 on September 20, 1995.

280 MM 10/05/95 08272271

1 117 370.00 CK

Edward P. Gamson
Edward P. Gamson



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

32/9
cm
11/14/95

Applicant: Zepedee et al.)
Serial No.: 08/272,271) Attorney Docket
Filed: November 21, 1990) PHA-0026P CON I
For: NON-A, NON-B, HEPATITIS VIRUS) (2673/61109)
ANTIGEN, DIAGNOSTIC METHODS AND)
VACCINES)
Examiner: D. C. Wortman)

RESPONSE

OCT 19 1995

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Official Action dated March 21, 1995, for which a Petition for an extension of time and its required fee are enclosed, please amend the above-identified application as follows.

IN THE CLAIMS

In claim 39, please cancel the word "structural", and replace it with the word --fusion--.

REMARKS

Reconsideration of the above-identified patent application is respectfully requested in view of the amendment above and the discussion that follows.

Claims 39 has been amended. Claims 35 and 39-46 are in the case and before the Examiner.

A. The Amendment

Claim 39 has been amended to recite that a fusion protein is contemplated. This amendment is supported as was the amendment to claim 35 so that the claim encompasses the CAP-B

fusion protein as had been intended. The Examiner is thanked for noting the discrepancy between Claims 35 and 39.

It is seen that no new matter has been added to the application from their amendment.

B. Rejection Under 35 U.S.C. §112,
Second Paragraph

Claims 39-46 were rejected for lack of a proper antecedent basis. It is believed that the present amendment that provides such a basis has made this rejection moot.

C. Rejections Under 35 U.S.C. §103

1. First Rejection

The pending claims were rejected as allegedly obvious over the combined teachings of Wang in view of Kuo et al. and further in view of Smith et al., Gene, 67:31-40 (1988). Wang, previously of record, teaches the assay use of synthetic peptides from HCV that encompass a longer domain than that claimed here and asserts that the peptides of her claims can be made by recombinant techniques, but has no enabling disclosure of such recombinants. Kuo et al. (Kuo), also previously of record, teaches use of the recombinant SOD-fusion protein C-100 antigen. The C-100 antigen is from a different HCV protein than the capsid sequence of these claims. Smith et al., a newly relied-on disclosure, teaches use of a vector that results in the production of recombinant fusion proteins that include the GST protein and a thrombin cleavage site that are present in a fusion protein of these claims.

The Action asserts that it "would have been obvious to one of ordinary skill in the art to produce the HCV core antigen peptide of Wang as a recombinant fusion protein..." This basis

for rejection cannot be agreed with and is respectfully traversed.

It is first submitted that contrary to the assertions of the Action, "the HCV core antigen peptide of Wang..." is not claimed. Rather, a much shorter antigenic peptide than disclosed by Wang is utilized here. That short, 20 residue, HCV peptide is neither taught nor suggested by Wang.

Indeed, the data provided with Dr. Helting's Declaration mailed on October 13, 1993 in the parental application illustrate the futility of use of Wang's disclosure against these claims. That Declaration points out that a recombinant peptide corresponding to the HCV capsid at positions 21-40 was unexpectedly useless as an antigen in that it showed "an almost negligible level of activity..." (Paragraph 17) under conditions where the fusion protein was quite active.

Thus, whether one used a chemical or biological recombinant synthesis for the antigen here is not relevant. The bare short peptide is not sufficiently antigenic by itself and must be used as a fusion protein. That result was not expected and could not be predicted inasmuch as other similarly sized peptides are useful antigens.

Third, the fact that the C-100 protein of Kuo works as an assay antigen to some degree as a fusion protein makes no prediction that another antigen form a different protein would also be useful. Thus, as noted previously, Kuo adds nothing to the Wang or Smith disclosures.

Turning now to Smith, it can be agreed that Smith teaches use of a GST fusion protein enhances ease in recovering a recombinant. However, Smith teaches that the GST portion of the expressed molecule is cleaved from the fusion protein (see, the Summary).

Thus, using the smith teachings, and given the proper suggestion that is absent here as to desired HCV sequence, a skilled worker might express a fusion protein containing a desired HCV 21-40 sequence linked to GST via linker residues and the thrombin or factor X_n cleavage sites. That worker would then cleave the HCV peptide from the rest of the fusion protein and arrive at essentially the non-functional peptide Dr. Helting discussed in the above-noted Paragraph 17. Use of that free species is not claimed here.

Inasmuch as one not knowing the appropriate HCV sequence to use would have no reason to purify a fusion protein, the fact that a GST-containing fusion protein may offer aid in purification does not suggest that such a fusion protein would also be useful as part of an antigen in an assay method. Not only is use as an antigen of such a construct neither taught nor suggested, but the reasonable assurance of success required for obviousness by In re O'Farrell, 7 USPQ 2d. 1673 (Fed. Cir. 1988) is totally absent here. In addition, as noted in In re Deuel, 34 USPQ 2d. 1210, 1215-1216 (Fed. Cir. 1995), knowledge of a method for making a chemical entity does not suggest the chemical entity itself.

Thus, summing the teachings and facts here, (1) Wang neither teaches nor suggests use of a peptide or fusion protein containing the HCV peptide portion recited in the claims; (2) the bare recombinant peptide is unexpectedly an ineffective antigen; (3) Kuo's suggestion that a recombinant fusion protein containing the C-100 antigen is useful in an assay contains no teaching that a fusion protein of another HCV protein as is claimed would be similarly useful; (4) Smith's teaching of use of a GST-containing fusion protein to obtain enhanced purity makes no suggestion that such a fusion protein would also be useful as an antigen in an

assay; and (5) Smith's complete teaching to make a GST-containing fusion protein, purify it and then cleave it to remove the GST portion here provides the useless, bare 21-40 peptide that does not work in an assay. This rejection should therefore be withdrawn.

2. Second Rejection

All of the claims were also rejected as allegedly obvious over the disclosures of Houghton et al. (Houghton; U.S. Patent No. 5,350,671) in view of Smith, above. Houghton teaches the entire DNA and putative amino acid residue sequence of HCV. Houghton also teaches that some SOD-containing recombinant fusion proteins such as those produced by clones CA279a and CA290a (residues 1-84 and 9-177, respectively; Table of column 83) immunoreact with antibodies to HCV (Fig. 65). Fig. 65 recites an otherwise unidentified clone CA259a as being active, which may be a typographical error in view of the column 83 disclosures.

A point missed by the Action and its several references to the Houghton figures and text is that Houghton has no suggestion to use the short HCV sequence that is claimed here. Rather, all of the Houghton immunologically active recombinants are about four to about eight times longer than is a sequence of the claims.

Smith is used as above, to replace Houghton's SOD with GST to obtain ease in purification. The comments above as to the lack of a teachings in Smith as to use of a GST-containing fusion protein in an assay antigen and Smith's teaching of cleavage to provide a bare peptide are repeated by reference.

Thus, one is left with a teaching that (1) a SOD-HCV fusion protein longer than Wang's is immunoactive combined with (2) Smith's use of GST in place of SOD is no more useful to a skilled worker in pointing the way to the claimed invention than

were the combined teachings of Wang, Kuo and Smith. This rejection should therefore be withdrawn.

D. Summary


Claim 39 has been amended. Each basis for rejection has been dealt with and made moot or otherwise overcome.

The application is therefore believed to be in order for allowance. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381


Enclosures

Petition for Extension of Time and fee

Welsh & Katz, Ltd.
135 South LaSalle Street
Suite 1625
Chicago, Illinois 60603-4302
Telephone: 312/781-9470

CERTIFICATE OF MAILING

I hereby certify that this Response, in duplicate, is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on September 20, 1995.



08/272271


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/272,271 07/08/94 ZEREDEE

S

NORTMAN EXAMINER

18N1/0123

 WELSH AND KATZ LTD
135 SOUTH LA SALLE STREET
SUITE 1625
CHICAGO IL 60603

ART UNIT PAPER NUMBER

1813

33

DATE MAILED: 01/23/96

 This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9/20/95 ☒ This action is made final.

 A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133
Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION1. ☒ Claims 35, 39-46 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-34, 36-38, 47-53 have been cancelled.3. ☐ Claims _____ are allowed.4. ☒ Claims 35, 39-46 are rejected.5. ☐ Claims _____ are objected to.6. ☐ Claims _____ are subject to restriction or election requirement.7. ☐ This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.8. ☐ Formal drawings are required in response to this Office action.9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.14. ☐ Other**EXAMINER'S ACTION**

Serial Number: 08/272271

-2-

Art Unit: 1813

Claims 35 and 39-46 remain pending and under examination at this time.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Serial Number: 08/272271

-3-

Art Unit: 1813

Claims 35 and ³⁶~~38~~-46 are rejected under 35 U.S.C. § 103 as being unpatentable over US patent 5,350,671 to Houghton et al. in view of Smith et al. for reasons of record.

Applicant has summarized the teachings of the prior art and argued that while Houghton teaches the immunoreactivity of certain SOD-containing recombinant fusion proteins, Houghton does not suggest the instantly claimed, shorter, HCV core sequence. Applicant has asserted that Smith does not teach using a GST-containing fusion protein as an assay antigen and that Smith teaches cleavage at the thrombin site to produce a peptide which Applicant now describes as non-functional for the purpose of immunoassays. Applicant urges that the Declaration of Dr. Helting dated October 13, 1993, shows unexpected results.

Applicant's arguments have been considered and Dr. Helting's Declaration has been considered again in light of the arguments as now presented. Neither the arguments nor the Declaration were found persuasive for the following reasons.

Houghton specifically exemplifies immunoreactivity of recombinant fusion proteins containing SOD and HCV core amino acid sequences, longer than, but including the instantly claimed sequence. While Houghton does not exemplify use of exactly the HCV sequence as instantly claimed, Houghton teaches that important epitopes are contained on shorter sequences and thus use of shorter sequences would have been obvious over Houghton. Smith provides motivation to substitute GST for SOD in a recombinant fusion protein because Smith discloses that GST fusion proteins can usually be purified under non-denaturing conditions and this is generally desirable. Smith teaches that the thrombin site may (not must) be used to cleave a peptide from the GST portion of the fusion protein but is not seen to teach away from leaving the fusion protein intact. In fact, Applicant's own specification teaches that the thrombin site

Serial Number: 08/272271

-4-

Art Unit: 1813

in the instantly claimed polypeptide may be used to cleave the HCV peptide ("structural protein") from the GST. For that same reason, Applicant's specification does not support the assertedly unexpected results of the cited Declaration since according to the specification, either the structural protein or the recombinant fusion protein may be used in assays (e.g., specification, page 6, lines 1-10; page 25, lines 18-30; the Abstract).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4065 and (703) 308-7939.

Any inquiry concerning this communication should be directed to Examiner Donna C. Wortman at telephone number (703) 308-1032.

Donna C. Wortman, Ph.D.
January 19, 1996

Mary Mosher
**MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800**



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.

Serial No.: 08/272,271

Filed: July 8, 1994

For: NON-A, NON-B HEPATITIS VIRUS
ANTIGEN DIAGNOSTIC METHODS
AND VACCINES

Examiner: D. Wortman

) Attorney Docket #34
) PHA 0026P CON I 5-5-96
) (2673/61109) Done

) Group Art Unit:
1813

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MAY 01 1996

GROUP 1800

ASSOCIATE POWER OF ATTORNEY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned attorney of record in the above-identified Patent Application hereby appoints Paul Lempel, Registration No. 21,198, as associate attorney in said application to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith. Mr. Paul Lempel's address and phone number are shown below.

Paul Lempel, Esq.
Kenyon & Kenyon
One Broadway
New York, New York 10004
Phone: 212/425-7200
Fax: 212/425-5288

Dated:

April 18, 1996

Edward P. Gamson
Edward P. Gamson
Registration No. 29,381

Enclosure
Change of Address

CERTIFICATE OF MAILING

I hereby certify that this Power of Attorney and a Change of Address, are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on April 18, 1996.

Edward P. Gamson
Edward P. Gamson



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Zebedee et al.)
Serial No.: 08/272,271) Attorney Docket
Filed: July 8, 1994) PHA 0026P CON I
For: NON-A, NON-B HEPATITIS VIRUS) (2673/61109)
ANTIGEN DIAGNOSTIC METHODS) Group Art Unit:
AND VACCINES) 1813
Examiner: D. Wortman)

#35
55-96
C. D. Home

CHANGE OF ADDRESS

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-entitled application, this is to notify you that our law firm, Welsh & Katz, Ltd., has moved from the old address of 135 South La Salle Street, Suite 1625, Chicago, Illinois 60603 to the following new address and phone numbers.

WELSH & KATZ, LTD.
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
Phone (312) 655-1500
Fax No. (312) 655-1501

Please forward correspondence regarding the above patent to counsel at the address given herein.

Respectfully submitted,

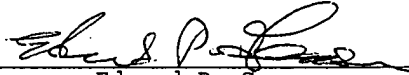
By Edward P. Gamson
Edward P. Gamson, Reg. No. 29,381
Attorney of Record

WELSH & KATZ, LTD.
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
Phone (312) 655-1500
Fax No. (312) 655-1501

Serial No. 08/272,271

CERTIFICATE OF MAILING

I hereby certify that this Change of Address together with a Associate Power of Attorney, are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on April 18, 1996.


Edward P. Gamson



#36

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Zebedee et al.
Serial No. : 08/272,271
Filed : July 8, 1994
For : NON-A NON-B HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHOD
AND VACCINES
Examiner : D.C. Wortman
Art Unit : 1813

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MAY 23 1996
GROUP 1800

Assistant Commissioner
for Patents
Washington, D.C. 20231

I hereby certify that this
AMENDMENT is being deposited with
the United States Postal Service
as first class mail in an
envelope addressed to Assistant
Commissioner for Patents,
Washington, D.C. 20231 on April
22, 1996.
Paul Lempel (Reg. No. 21,198)

AMENDMENT (FIRST SUBMISSION) UNDER 37 C.F.R. 1.129(a)

SIR:

Reconsideration is requested of the rejection of claims 35, 39-46 as obvious under 35 U.S.C. § 103 over Houghton et al. (U.S. Patent No. 5,350,671), in view of Smith et al., Gene, 67, at 31-40, (1988), as set forth in the Office action mailed January 23, 1996.

Applicants respectfully submit that the prior art does not suggest or motivate one of ordinary skill in this art to make the amino acid sequence set forth in the rejected claims. There is no suggestion that the sequence discovered by applicants, namely the sequence of amino acids 21-40 of the capsid protein of NANBV, should

be made or used for detecting the presence of antibodies against NANBV in a body fluid sample.

The prior art having failed to disclose or suggest the herein claimed sequence, a prima facie case of obviousness has not been established. The claims are therefore allowable. Applicants set forth below their position in greater detail.

The prior art primarily relied upon by the Examiner is the '671 patent to Houghton, et al., which describes certain protein sequences of the Non-A, Non-B virus (NANBV), also referred to as the hepatitis C virus (HCV). In particular, the '671 patent describes the complete sequence of the variant of NANBV known as CDC/HCV1, which contains over 3000 amino acids. A number of overlapping subregions of the sequence were expressed in E. coli as fusions to superoxide dismutase (SOD) to indicate which of these polypeptides bound to antibodies for NANBV, and how frequently such antibodies were found in sera of a number of NANBV positive individuals. Two subregions which bound to serum antibodies of NANBV infected individuals contained sequences from the capsid and envelope proteins. One subregion consists of a protein fragment having amino acids 1-84 of the entire CDC/HCV1 variant, and the second subregion consists of fragment having amino acids 9-177.

The '671 patent described polypeptides that overlap the capsid region (i.e., amino acids 1-120) that consist of amino acids 1-10, or 1-25, or 1-50, or 5-20,

or 20-25, or 35-45, or 40-90, or 45-65, or 50-100, or 65-75, or 80-90, or 95-110, or 99-120, or 100-150, or 105-120. None of these polypeptides is the herein claimed subregion amino acids 21-40, nor is claimed subregion amino acids 21-40 suggested. The '671 patent also claims that peptide fragments of at least 8 contiguous amino acids from amino acids 1-177 may be used in an immunoassay for detecting antibodies that bind to NANBV. The patentee's basis for these descriptions (other than amino acids 1-84, and 9-177) is unknown.

The claims of the pending application, S.N. 272,271, set forth the polypeptide sequence from the viral capsid protein that is amino acids 21-40. This polypeptide is not described or suggested by the '671 patent.

The Examiner has rejected the instant claims as obvious, and stated that the '671 patent exemplifies "HCV core amino acid sequences, longer than, but including the instantly claimed sequence. While Houghton does not exemplify use of exactly the HCV sequence as instantly claimed, Houghton teaches that important epitopes are contained on shorter sequences and thus use of shorter sequences would have been obvious over Houghton." [Office action, at 3]. The Examiner has also declined to accept Applicants' assertion of unexpected results. [Id., at 4].

It is respectfully submitted that the Examiner's position is not sustainable, because a prima facie case of obviousness has not been made out. Therefore, the

claims are allowable, and the matter of "unexpected results" does not arise. The Examiner has conceded that the description in the '671 patent does not describe the amino acids 21-40 peptide. Neither does any part of the '671 specification suggest amino acids 21-40.

Furthermore, we have calculated that the 120 amino acids of the capsid protein would have to be broken into about 6500 different sequences (and over 13,000 sequences if chosen from the broader Houghton, et al. range of amino acids 9-177) of 8 or more amino acids in order that the herein claimed amino acids sequence of 21-40 be made. Even if that extremely laborious job were to have been accomplished by one of ordinary skill, there would still be no suggestions or motivation in the prior art to select Applicants' sequence, and then to discover its immunoreactive properties, as Applicants did. As conceded by the Examiner, Smith et al. does not fill in the void left by the '671 patent with respect to the claimed amino acids 21-40 sequence.

The following cases support Applicants' position: In re Brouwer, 37 U.S.P.Q.2d 1663 (CAFC 1996); In re Deuel, 34 U.S.P.Q.2d 1210 (CAFC 1995); In re Baird, 29 U.S.P.Q.2d 1550 (CAFC 1994); In re Bell, 26 U.S.P.Q.2d 1529 (CAFC, 1993); Bristol-Meyers Co. v. U.S.I.T.C., 15 U.S.P.Q.2d 1258 (CAFC 1989); In re Kuehl, 475 F.2d 658 (CCPA 1973).

In summary, the prior art fails to describe or suggest Applicants' amino acids sequence of 21-40, and

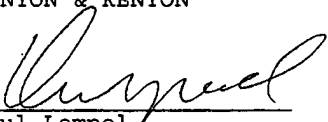
therefore, a prima facie case of obviousness has not been established. In the absence of a prima facie case of obviousness, there is no burden on Applicants to rebut the Examiner's position by a showing of "unexpected results."

Reconsideration of the rejection is requested and a Notice of Allowance is solicited.

Respectfully submitted,

KENYON & KENYON

DATED: April 22, 1996


Paul Lempel
Reg. No. 21,198

Attorney for Applicants
One Broadway
New York, N.Y. 10004
(212) 425-7200



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Zebedee et al.
Serial No. : 08/272,271
Filed : July 8, 1994
For : NON-A NON-B HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHOD
AND VACCINES
Examiner : D.C. Wortman
Art Unit : 1813

RECEIVED
MAY 23 1996
GROUP 1800

Assistant Commissioner
for Patents
Washington, D.C. 20231

I hereby certify that this
TRANSMITTAL is being deposited
with the United States Postal
Service as first class mail in an
envelope addressed to Assistant
Commissioner for Patents,
Washington, D.C. 20231, on April
22, 1996.

Paul Lempel (Reg. No. 21,198)

TRANSMITTAL OF AMENDMENT UNDER 37 C.F.R. § 1.129(a)

SIR:

Please find an Amendment transmitted herewith
for filing in the above-identified patent application.

In response to the Final Rejection dated
January 23, 1996, please enter this first Submission
under 37 C.F.R. § 1.129(a). Since this application has
an effective pendency of at least two years as of June 8,
1995, taking into account prior applications under 35
U.S.C. §§ 120, 121 and 365(c), and since this First
Submission is being filed prior to the filing of an
Appeal Brief, the finality of the outstanding January 23,
1996 Final Rejection should be withdrawn automatically.
010 UJ 11-0600 04/29/96 08272271
1000-146 250.00CH

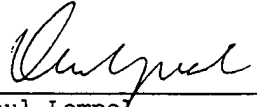
Please charge the \$750.00 fee as set forth in

\$1.17(r) to Deposit Account No. 11-0600. If any additional fees are due, please charge Deposit Account No. 11-0600. A duplicate copy of this transmittal letter is enclosed for that purpose.

Respectfully submitted,

KENYON & KENYON

Dated: April 22, 1996


Paul Lempel
Reg. No. 21,198

One Broadway
New York, New York 10004
(212) 425-7200

08/272271


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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08/272,271 07/08/94 ZEBEDEE

S

 EXAMINER
WORTMAN, D

18N1/0806

 WELSH AND KATZ LTD
120 SOUTH RIVERSIDE PLAZA, 22ND FLOOR
CHICAGO, ILLINOIS 60606

ART UNIT	PAPER NUMBER
----------	--------------

 1813
DATE MAILED:

37

08/06/96

 This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS
OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 4/22/96
- ☒ This action is **FINAL**.

- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 35, 39-46 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 35, 39-46 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s) _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

Serial Number: 08/272271

-2-

Art Unit: 1813

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on April 22, 1996, has been entered.

Claims 35 and 39-46 remain pending and under examination at this time.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Serial Number: 08/272271

-3-

Art Unit: 1813

Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 35 and 38-46 are rejected under 35 U.S.C. § 103 as being unpatentable over US patent 5,350,671 to Houghton et al. in view of Smith et al. for reasons of record.

Applicant has argued that the art of record does not suggest or motivate one of ordinary skill in the art to make the amino acid sequence set forth in the rejected claims and that in particular, there is no suggestion to make and use amino acids 21-40 of NANBV capsid protein for detecting antibodies.

Applicant has reviewed the teachings of Houghton regarding making fusion proteins containing amino acids 1-84 and amino acids 9-177 and describing several polypeptides from the capsid (or core) region and has asserted that none of the specifically named polypeptides are amino acids 21-40. Applicant asserts that the instant claims are not obvious because one would have to make several thousands of different sequences, based on starting with a capsid peptide consisting of amino acids 1-120 in order to include the instantly claimed sequence and that even if one did make the sequence, there is no suggestion or motivation to select the instant sequence as being immunoreactive. Applicant concludes that no case for obviousness has been established.

These arguments have been considered but not found persuasive. It is agreed that Houghton does not anticipate Applicant's claimed invention; however, the rejection of record was made under 35 U.S.C. § 103 and not under 35 U.S.C. § 102. Moreover, Houghton is available for everything taught therein and not merely its working examples. Houghton presents extensive teachings regarding the use of HCV core sequences of different sizes and the use of HCV antigen fusion proteins to detect HCV antibodies and points out that epitopes are present on all the peptides listed at col. 28, line 67-col.

Serial Number: 08/272271

-4-

Art Unit: 1813

29, line 68, including the peptide which contains AA1-AA50. Further, Houghton teaches how to screen peptides for immunoreactivity using methods disclosed as routine (col. 28, lines 30-41) to better determine the location of the epitope of interest once a longer peptide containing the epitope has been identified. Houghton also discloses use of HCV amino acid sequences shorter than those mentioned by applicant (i.e., those containing amino acids 1-120 or amino acids 1-84 and amino acids 9-177) to make fusion proteins, e.g. at col. 27, line 66-col. 28, line 10. Thus an epitope-containing peptide containing HCV capsid amino acids 21-40 is seen to be obvious over the teachings of Houghton. Smith teaches making recombinant fusion proteins using GSH and was relied upon for that teaching; the rejection was made over the combination of references.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.129(a) and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.129(a). Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the submission under 37 CFR 1.129(a). See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Since the fee set forth in 37 CFR 1.17(r) for a first submission subsequent to a final rejection has been previously paid, applicant, under 37 CFR 1.129(a), is entitled to have a second submission entered and considered on the merits if, prior to abandonment, the second submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a second submission and the appropriate fee of \$750 for a large entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

Serial Number: 08/272271

-5-

Art Unit: 1813

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center numbers are (703) 308-4065 and (703) 308-7939.

Any inquiry concerning this communication should be directed to Examiner Donna C. Wortman at telephone number (703) 308-1032.

Donna C. Wortman, Ph.D.
August 1, 1996



MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800



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#38
lm
10/25/96

SECOND SUBMISSION.
UNDER 37 C.F.R. §1.129(a)
Expedited Procedure
Examining Group 1813

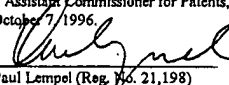
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Zebedee et al.
Serial No. : 08/272,271
Filed : July 8, 1994
For : NON-A NON-B HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHOD
AND VACCINES
Examiner : D. C. Wortman
Art Unit : 1813

GROUP 180
OCT 21 AM 10:26

Assistant Commissioner
for Patents
Washington, D.C. 20231

I hereby certify that this SECOND SUBMISSION UNDER 37
C.F.R. §1.129(a) TO FINAL REJECTION is being deposited with
the United States Postal Service as first class mail in an envelope
addressed to Assistant Commissioner for Patents, Washington, D.C.
20231, on October 7, 1996.


Paul Lempel (Reg. No. 21,198)

SECOND SUBMISSION UNDER 37 C.F.R. §1.129(a) TO FINAL REJECTION

Sir:

Reconsideration is requested of the final rejection of
claim 35, 39-46 as obvious under 35 U.S.C. §103 over Houghton et
al. (U.S. Patent No. 5,350,671), in view of Smith et al. (Gene,
67, at 31-40, (1988)), as set forth in the Office action mailed
August 6, 1996. A second fee under 37 C.F.R. §1.129(a), in the
amount of \$770.00 pursuant to 37 C.F.R. §1.17(r), is enclosed.
Withdrawal of the final rejection is therefore automatic.

Applicants demonstrate in this Response that the

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Examiner has not established a prima facie case of obviousness. For the reasons stated herein, Houghton's extensive teaching fails to render obvious the use of Applicants' sequence of amino acids 21-40 of the viral caspid protein of NANBV. In fact, even if one skilled in the art were to carry out the enormous research project in Houghton, (see infra), such person would not be led to Applicants' 21-40 amino acid sequence, would fail to recognize the surprisingly high immunoreactivity of Applicants' 21-40 amino acid sequence, and would discover that Houghton teaches away from the use of Applicants' 21-40 amino acid sequence. Therefore, Applicants' claims 35, 39-46, that recite the 21-40 amino acid sequence, are patentable and should be allowed.

In Applicants' Response of April 22, 1996 to the Office action mailed January 23, 1996, it was pointed out that the Houghton patent description calls for a substantial amount of work to be carried out in order to make all the shorter sequences based on AA1-AA177, but Houghton does not provide a motive to select and use Applicants AA21-AA40 sequence.

Again conceding that Houghton does not anticipate Applicants' invention, the Examiner has now finally rejected the instant claims relying on a series of procedures from Houghton that the Examiner maintains leads to Applicants' AA21-AA40 polypeptide. First, the Examiner observed that, "Houghton presents extensive teachings regarding the use of HCV core sequences of different sizes . . . and points out that epitopes are present on all the peptides listed at col. 28, line 67 - col.

29, line 68 including the peptide which contains AA1-AA50".

(Emphasis added.) Office action, at 3-4. The Examiner next relied on Houghton for the teaching of, "how to screen peptides for immunoreactivity using methods disclosed as routine (col. 28, lines 30-41) to better determine the location of the epitope of interest['] once a longer peptide containing the epitope has been identified." (Emphasis added.) Id. at 4. Finally, the Examiner stated that Houghton, "also discloses use of HCV amino acid sequences shorter than those mentioned by applicant[s] (i.e., those containing [sic, "contained in"(?)] amino acids 1-120 or amino acids 1-84 and amino acids 9-177) to make fusion proteins, e.g. at col. 27, line 66 - col. 28, line 10." (Emphasis added.) Id.² The Examiner thereupon concluded that, ". . . an epitope-containing peptide containing HCV caspid amino acids 21-40 is seen to be obvious over the teachings of Houghton." Id.

It is respectfully contended that the Examiner has failed to consider the descriptions in Houghton that make it clear that Applicants' claimed method of use of AA21-AA40 is not suggested by this reference. Therefore, the Examiner has not made out a prima facie case of obviousness, and the rejection

¹ "Epitope of interest" would appear to refer to, "a purified polypeptide comprising an epitope which is immunologically identifiable with an epitope contained in HCV." See Houghton '671 patent, column 6, lines 19-21.

² Because Applicants "mentioned" all sequences that are described by Houghton at column 28, line 67 - column 29, line 68 and overlap AA1-AA120, Applicants assume that the Examiner is referring to 5mer peptides described by Houghton at column 27, lines 4-7, column 27, lines 59-66, and column 28, lines 22-24.

should be withdrawn. In re Brouwer, 37 U.S.P.Q. 2d 1663, 1666 (Fed. Cir. 1996).

First, the Examiner's statement that Houghton points out that the different size peptides in columns 28 and 29 all contain epitopes, appears to be inconsistent with Houghton's description. The 188 peptides listed at column 28, line 67 - column 29, line 68 are not identified as "all" containing epitopes. Houghton states, "It is to be understood that these peptides do not necessarily precisely map one epitope, but may also contain HCV sequence that is not immunogenic". (Emphasis added.) Col. 28, lines 55-59. This comment, in view of Houghton's subsequent specific descriptions, means that the list at columns 28 and 29 includes peptide sequences that are not immunogenic. Specifically, at column 83, the table identifies only 17 of 188 sequences shown in the list on columns 28 and 29 as having "proven reactivity with sera from NANBH patients," (col. 83, line 35; see also col. 22, lines 13-16), and Figure 63 shows 16 of these 17 antigenic sequences as cross-hatched bars, and the remaining clear bars are understood to be non-antigenic sequences or not expressed. The locations of these 16 or 17 sequences vary between AA1 (as the starting amino acid of the earliest sequence) and AA2886 (as the final amino acid of the last sequence). Id. at lines 39, 52. These sequences span virtually the entire viral protein sequence of about 3000 amino acids. Moreover, AA1-50 is not listed in the table on column 83 (or Figure 63) as having "proven reactivity". Therefore, one

skilled in the art reading the Houghton patent as a whole is not directed to or enlightened with respect to Applicants' polypeptide sequence of AA21-AA40. In actuality, rather than narrowing the scope of the search for Applicants' sequence of AA21-AA40, these descriptions teach a person skilled in this art that immunogenic sequences are found across the entire 3000 amino acid span of the viral sequence.

Second, as shown herein, the method described by Houghton for preparing and screening for purified polypeptides that include epitopes which are immunologically identifiable with epitopes contained in HCV requires countless hours of experimentation and carrying out many thousands of experiments. At the end of the day none of those experiments would suggest one polypeptide over another, and certainly would not suggest Applicants' polypeptide of AA21-AA40. The screening description in column 28, lines 30-41 states that, "Truncated HCV amino acid sequences comprising the epitopes can be identified" This statement means that various sequences can be identified, but it says nothing about selecting a specific sequence, much less Applicants' immunogenically enhanced specific sequence, AA21-AA40. The description in column 28 continues, "the entire viral sequence [as shown in Houghton Figure 66] can be screened by preparing a series of short peptides" (Emphasis added.) This means screening short peptides of a protein having at least 3,000 amino acids. The description goes on to state that the series of short peptides "together span the entire

protein sequence." (Emphasis added.) Houghton teaches that 100mer polypeptides, derived from the entire viral sequence of 3,000 amino acids, should be "routinely tested" for the "presence of epitope(s) showing a desired reactivity, and then testing progressively smaller and overlapping fragments from identified 100mer to map the isotope of interest." (Emphasis added.) Col. 28, lines 36-39. In order for a person of ordinary skill in the art to carry out Houghton's screening procedure, such a person would first have to prepare approximately 30 polypeptide sequences of 100 amino acids each. Following the description in Houghton, that person would then test "progressively smaller and overlapping fragments" of each 100mer polypeptide down to 5mer sequences, because as Houghton states, "Fragments of as few as 5 amino acids may characterize an antigenic region,"; (col. 27, lines 6-7), and, "Typically, the truncated HCV amino acid sequence will range from about 5 to about 100 amino acids in length." Col. 28, lines 22-24.

"Progressively smaller fragments" calculates to about 136,800 "smaller" sequences.³ Moreover, following Houghton's

³ In order to ensure that all sequences of 5 amino acids up to 100 amino acids over the span of 3000 amino acids are prepared for screening -- including Applicants' AA21-AA40 -- "progressing" down from sequences of 100mers to sequences of 5mers for each of the 30 polypeptides having 100mers, one adds all sequences in each series beginning with the sequences in the series for AA100-AA1, AA99-AA1, AA98-AA1, . . . AA5 - AA1, and going through each "progressively smaller" series, i.e., AA100-AA2, AA99-AA2, AA98-AA2, . . . AA6-AA2 down to the last one-member series, AA100-AA96. This adds up to 4560 sequences for each 100mer sequence in the 3000 amino acid viral sequence, or 30 x 4560, which is 136,800 sequences.

directions to prepare "overlapping fragments" would substantially increase this figure. Assuming that one skilled in the art, working continuously on this project could reasonably prepare ten of these sequences per day, it would take such a person 13,680 days (or over 35 years) to merely prepare the number of "progressively smaller" sequences called for by Houghton. (This estimate does not include preparing "overlapping fragments.") Screening of the peptide sequences, according to Houghton in column 28, lines 30-39, merely identifies the presence or absence of epitopes which are immunologically identifiable with epitopes contained in HCV. Thus, although a great deal of time would be consumed following the Houghton procedures, at the end of this time, one skilled in the art would be no closer to Applicants' AA21-AA40 sequence than that person would be before embarking on this 35-year project.

Although not referred to by the Examiner, Houghton suggests another (theoretical) method by which the entire viral protein sequence may be analyzed to identify potential epitopes for screening, perhaps to save time. Col. 28, lines 41-53. Houghton refers to Figure 67 where the hydrophilic/hydrophobic character of the HCV amino acid sequence is displayed above the antigen index. See also col. 109, line 55 - col. 110, line 10. Figure 67 plots the entire 3,000+ amino acid sequence of the viral protein. Again, there is no suggestion in Figure 67 to one of ordinary skill in the art to select Applicants' sequence of AA21-AA40. However, even if one of ordinary skill in the art

were by some unknown process able to divine Applicants' AA21-AA40 polypeptide, reference to Figure 67A would demonstrate to the person of ordinary skill that such a polypeptide is predominantly below the line, thus predicting poor antigenicity. Col. 110, lines 4-8. Consequently, if one of ordinary skill tried to take this "shortcut" to save 35 years, the person would be led away from using Applicants' amino acid sequences of AA21-AA40.

Third, the Examiner, perhaps recognizing the enormous amount of experimentation that would have to be carried out by one of ordinary skill to prepare and screen the polypeptides, turned to the Houghton description of "fusion proteins". The Examiner commented that Houghton "also" discloses that "shorter" sequences [or "truncated" sequences (col. 27, line 60-61)] -- presumably sequences of about "5 amino acids" (col. 27, line 6; and col. 28, line 23), and presumably sequences that contain an epitope (col. 27, line 7; line 61; and lines 17-18) -- can be expressed as a fusion protein.⁴ In this connection, Houghton states that, "While this truncated sequence can be produced by various known treatments of native viral protein, it is generally preferred to make . . . HCV sequences and heterologous sequences in a fusion protein." (Emphasis added.) Col. 27, line 66 - col. 28, line 6. This statement means that the Houghton fusion protein is made up of the truncated HCV 5-amino acid sequences fused to heterologous amino acid sequences. The results of such

⁴ Sequences of 5mers based on the entire viral sequence of 3,000 amino acids calculates to 2996 5mer sequences.

fusion, therefore, cannot be Applicants' fused polypeptide sequence that contains the HCV 20-amino acid sequence AA21-AA40. Moreover, having information about 5mer sequences does not provide information about longer sequences.

Therefore, for the reasons stated herein, the Examiner's conclusion that Applicants' "epitope-containing peptide containing HCV caspid amino acids 21-40 is seen to be obvious over the teachings of Houghton" is not sustainable. Upon analysis, it is recognized that Houghton fails to suggest the use of Applicants' amino acid sequence AA21-AA40; fails to teach a method that would lead to Applicants' polypeptide sequence; and fails to suggest a reason for selecting AA21-AA40. Smith fails to fill in Houghton's missing descriptions.

Applicants again invite the Examiner to the following Federal Circuit cases that support Applicants' legal position. In re Brouwer, 37 U.S.P.Q. 2d 1663, 1666 (Fed. Cir. 1996) is controlling authority because, as shown herein, Houghton has not "suggested" the use of Applicants' AA21-AA40 sequence to practice the herein claimed method. (" . . . [T]he mere possibility that one of the [materials used by Houghton] could be modified or replaced such that its use would lead to the specific [AA21-AA4 sequence] recited in [Applicants' claims] does not make the [Applicants' claimed method] obvious 'unless the prior art suggested the desirability of such a modification' or replacement [citation omitted] Without first knowing [Applicants'] claimed [method], . . . there is simply no suggestion in the

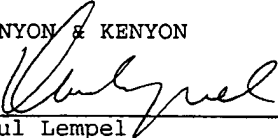
[Houghton] reference . . . to practice the claimed [method].
[Applicants' claimed method] is therefore not prima facie
obvious." See also In re Deuel, 34 U.S.P.Q.2d 1210 (Fed. Cir.
1995); In re Baird, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994); In re
Bell, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993); Bristol-Meyers Co. v.
U.S.I.T.C., 15 U.S.P.Q.2d 1258 (Fed. Cir. 1989); In re Kuehl, 475
F.2d 658 (Fed. Cir. 1973); In re Jones, 21 U.S.P.Q.2d 1941 (Fed.
Cir. 1992).

Because the Examiner has not made out a prima facie
case of obviousness there is no burden on Applicants to rebut the
Examiner's position. In re Deuel, 34 U.S.P.Q. 2d at 1214.

Reconsideration of the rejection is requested and a
Notice of Allowance is solicited.

Respectfully submitted,

KENYON & KENYON


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Attorney for Applicants
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(212) 425-7200

Dated: October 7, 1996



#39
10/25/96
lm

SECOND SUBMISSION
UNDER 37 C.F.R. §1.129(a)
Expedited Procedure
Examining Group 1813

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Zebedee et al.
Serial No. : 08/272,271
Filed : July 8, 1994
For : NON-A NON-B HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHOD
AND VACCINES
Examiner : D. C. Wortman
Art Unit : 1813

56 OCT 21 AM 10:26
GROUP 180

Assistant Commissioner
for Patents
Washington, D.C. 20231

I hereby certify that this TRANSMITTAL OF SECOND
SUBMISSION UNDER 37 C.F.R. §1.129(a) TO FINAL
REJECTION is being deposited with the United States Postal
Service as first class mail in an envelope addressed to Assistant
Commissioner for Patents, Washington, D.C. 20231, on October 7,
1996.

Paul Lempel
Paul Lempel (Reg. No. 21,196)

TRANSMITTAL OF SECOND SUBMISSION
UNDER 37 C.F.R. §1.129(a) TO FINAL REJECTION

Sir:

Please find the SECOND SUBMISSION UNDER 37 C.F.R.

§1.129(a) TO FINAL REJECTION transmitted herewith for filing in
the above-identified patent application.

In response to the final rejection mailed August 6,
1996, please enter the attached SECOND SUBMISSION UNDER 37 C.F.R.
§1.129(a). The finality of the August 6, 1996 final rejection
should be withdrawn automatically.

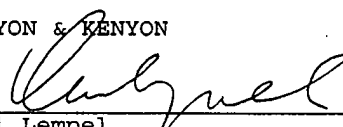
Please charge the \$770.00 fee as set forth under 37

C.F.R. §1.17(r) to Deposit Account No. 11-0600. If any additional fees are due, please charge Deposit Account No. 11-0600. A duplicate copy of this transmittal letter is enclosed for that purpose.

Respectfully submitted,

KENYON & KENYON

Dated: October 7, 1996



Paul Lempel
Reg. No. 21,198
Attorney for Applicants
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New York, New York 10004
(212) 425-7200

08/272271


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/272,271	07/08/94	ZEBEDEE	5

 18M1/0106
 WELSH AND KATZ LTD
 120 SOUTH RIVERSIDE PLAZA, 22ND FLOOR
 CHICAGO IL 60606

EXAMINER	
WORTMAN, D	
ART UNIT	PAPER NUMBER
1815	40

DATE MAILED: 01/06/97

 This is a communication from the examiner in charge of your application.
 COMMISSIONER OF PATENTS AND TRADEMARKS
OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 10/7/96
- ☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 35 and 39-46 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 35 and 39-46 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

Art Unit: 1815

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on October 7, 1996, has been entered.

Claims 35 and 39-46 remain pending and under examination at this time.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 35 and 38-46 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US patent 5,350,671 to Houghton et al. in view of Smith et al. for reasons of record.

Applicant has urged that Houghton's teachings do not render obvious the use of applicant's NANB viral capsid protein amino acid sequence 21-40. Applicant contends that even if one were to carry out procedures taught by Houghton, one would not be led to the instantly claimed sequence, would fail to recognize the "surprisingly high immunoreactivity," and would discover that Houghton teaches

Art Unit: 1815

away from the use of the 21-40 amino acid sequence. Applicant argues that Houghton's disclosure of peptides at col. 28, line 67-col. 29, line 68, does not identify all of the listed peptides as containing epitopes, and points to col. 83 as indicating that only some of the peptides immunoreact with sera from NANBH patients. Applicant argues that the peptides shown to be immunoreactive span the entire viral protein sequence of about 3000 amino acids. Applicant urges that the procedures described in Houghton for screening for epitopes in all the truncated peptides of 5-100 amino acids based on the disclosed sequences would require many years. Further, although the rejection of record does not rely on the portion of Houghton's disclosure regarding prediction of antigenicity by hydrophilicity, Applicant points out that one attempting to predict antigenicity by this method would be led away from the instantly claimed sequence. Applicant argues that Houghton's disclosure regarding the desirability of fusion proteins applies to 5-mers and thus cannot lead to the instantly claimed 20 amino acid NANBV sequence. Applicant cites, among others, *In re Brouwer* 37 USPQ 2d 1663, 1666.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons. The Examiner has interpreted the discussion (col. 28, lines 55-58) of the sequences disclosed beginning at col. 28, line 67, as indicating that each of the sequences listed, including AA1-AA50, contains an epitope and possibly some sequence that is not immunogenic; further, Houghton suggests deleting anything that is not immunogenic (col. 28, lines 58-61) and discloses how to screen the shorter peptides. Houghton also discloses that HCV sequences selected are desirably "at least about 10, 12, or 15 amino acids, up to a maximum of about 20 or 25 amino acids" (col. 28, lines 27-29).

Art Unit: 1815

Clearly Applicant's twenty amino acid peptide falls within the specific teachings of Houghton. Thus the prior art does suggest making the modification that would result in the claimed peptide. While some work would be necessary in order to determine how much of the AA1-AA50 peptide may be deleted and still retain immunogenicity, such screening of synthetic peptides was known in the art at the time the invention was made, was disclosed by Houghton, and was routinely done at the time the invention; absolute predictability is not required of the prior art but rather reasonable expectation for success. Such is provided by the disclosure of Houghton when taken as a whole. There would be no reason for one of skill in the art, based on Houghton's disclosure, to undertake to make and screen every possible peptide from the entire 3000 amino acid HCV polypeptide. Applicant's remarks regarding prediction of antigenicity by hydrophilicity are not believed germane to the rejection of record. Applicant's assertion that Houghton's disclosure regarding fusion proteins applies only to 5-mers is not understood since a thorough reading of Houghton (e.g., col. 28, lines 2-6) makes it clear that any of the truncated sequences containing one or more epitopes may be part of a fusion protein. Applicant's reliance on *In re Brouwer* is not completely understood, since the facts of the instant case differ from those in *In re Brouwer* which dealt with a process for the preparation of a catalyst in which one of the references taught only a generic method for making the required chemical substitution. The instant case, however, involves a method of use of an NANBV (HCV) capsid peptide fusion protein for detection of NANBV antibodies; the cited reference, Houghton, deals with HCV antigenic peptides of different sizes, which may be in the form of fusion proteins, and teaches that the specifically disclosed antigenic sequences may be routinely modified so as to delete the non-

Serial Number: 08/272271

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immunogenic sequence, thus establishing the desirability of making the necessary modification to arrive at the claimed invention.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.129(a) and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.129(a). Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the submission under 37 CFR 1.129(a). See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-7939.

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Page 6

Art Unit: 1815

Any inquiry concerning this communication should be directed to Examiner
Donna C. Wortman at telephone number (703) 308-1032.

Da

Donna C. Wortman, Ph.D.
December 31, 1996

Marian C. Knode
MARIAN C. KNODE
SUPERVISORY PATENT EXAMINER
GROUP 1800

44
PATENT
555467/61

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : Zebede et al.
Serial No. : 08/272,271
Filing Date : July 8, 1994
For : NON-A, NON-B, HEPATITIS VIRUS ANTIGEN,
DIAGNOSTIC METHODS AND VACCINES
Examiner : D. Wortman
Art Unit : 1815
Assistant Commissioner for
Patents
Washington, D.C. 20231

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SIR:

The undersigned attorney of record hereby gives to Denise English and Trung Thai, the power to inspect and make copies of the above-identified patent application file and the files of all continuations, divisions, reissues, substitutes, renewals, continuations-in-part thereof.

Respectfully submitted,

KENYON & KENYON

Date June 6, 1997

Paul Lempel by M. Lisa Wilson
Paul Lempel
Reg. No. 21,198

M. Lisa Wilson
Reg. No. 34,045

One Broadway
New York, New York 10004
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Facsimile: (212) 425-5288



U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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GROUP 1800

#42
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7/21/97

**REQUEST FOR EXTENSION OF TIME
PURSUANT TO 37 C.F.R. § 1.136(a)**

Docket Number:
55467/61

Application Number
08/272,271

Filing Date
July 8, 1994

Examiner
Wortman

Art Unit
1813

Invention Title
NON-A, NON-B HEPATITIS VIRUS ANTIGEN,
DIAGNOSTIC METHOD AND VACCINES

Inventor(s)
ZEBEDEE et al.

Address to:
Assistant Commissioner for Patents
Washington D.C. 20231

I hereby certify that this correspondence is being deposited with the
United States Postal Service as first-class mail in an envelope addressed
to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

Date: 7 July 1997

Reg. No. 26,170

Signature:

Arthur D. Gray
Arthur D. Gray
by Arthur D. Gray
Reg. No. 34,045

Applicant respectfully requests a three month extension of time in which to respond
to the office action dated January 6, 1997, for which a response period expiring on April
6, 1997 was set. The extended period expires on July 7, 1997.

1. The Commissioner is hereby authorized to charge payment of the 37 C.F.R. §
1.136(a) extension fee of \$930.00 to the deposit account of **Kenyon & Kenyon**,
deposit account number **11-0600**.
2. A duplicate copy of this form is enclosed.

Dated: 7 July 1997

By:

Arthur D. Gray
Arthur D. Gray (Reg. No. 26,170)
by Arthur D. Gray
Reg. No. 34,045

KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
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07/18/1997 RJOHNSON 00000066 DAW:110600 08272271
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BOX AF

01813

PATENT
Docket No. 55467/61

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): ZEBEDEE et al

Serial No.: 08/272,271

Filing Date: July 8, 1994

For: NON-A NON-B HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHOD
AND VACCINES

Group Art Unit: 1813

Examiner: Wortman, D.C.

18c

RECEIVED
JUL 21 1997
GROUP 1800

Address to:
Assistant Commissioner for Patents
Washington D.C. 20231

I hereby certify that this correspondence is being deposited with the
United States Postal Service as first class mail in an envelope addressed
to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

Date: July 7, 1997

Reg. No. 26,170

Signature: Arthur D. Gray by M. J. Hill
Arthur D. Gray N. 34, 045

NOTICE OF APPEAL

Applicant hereby appeals to the Board of Patent Appeals and Interference from the decision of the Examiner made in the Final Office Action dated January 6, 1997, finally rejecting claims 35 and 39-46.

1. The Commissioner is hereby authorized to charge payment of the 37 C.F.R. § 1.191 Notice of Appeal fee of \$300.00 to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**. The Commissioner is also authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 11-0600.
2. A petition for extension of time is enclosed.
3. A duplicate copy of this communication is enclosed for charging purposes.

07/18/1997 Dated: July 7, 1997
01 FC:119 RICHARDSON 00000087 DAN:110600 08272271
300.00 CH

By: Arthur D. Gray by M. J. Hill
Arthur D. Gray (Reg. No. 26,170) N. 34, 045

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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

AMENDMENT TRANSMITTAL LETTER

Docket Number:
55467/61

Application Number
08/272,271

Filing Date
July 8, 1994

Examiner
Wortman

Art Unit
1813

Invention Title
NON-A, NON-B HEPATITIS VIRUS ANTIGEN,
DIAGNOSTIC METHOD AND VACCINES

Inventor(s)
ZEBEDEE et al et al.

Address to:
Assistant Commissioner for Patents
Washington D.C. 20231

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Date: 7 July 1997

Reg. No. 26,170

Signature: Arthur D. Gray by Arthur D. Gray
Arthur D. Gray (Reg. No. 26,170) by No. 34,045

Transmitted herewith is an amendment in
the above-identified application.

1. Other enclosures:
Notice of Appeal, and
Three Month Extension of Time
2. No additional fee for this Amendment is required.
3. The Commissioner is hereby authorized to charge payment of the following fees
associated with this communication or credit any overpayment to the deposit
account of **Kenyon & Kenyon**, deposit account number 11-0600:
 - A. Any additional filing fees required under 37 C.F.R. § 1.16;
 - B. Any additional patent application processing fees under 37 C.F.R. § 1.17;
 - C. Any additional patent issue fees under 37 C.F.R. § 1.18;
 - D. Any additional document supply fees under 37 C.F.R. § 1.19;
 - E. Any additional post-patent processing fees under 37 C.F.R. § 1.20; or
 - F. Any additional miscellaneous fees under 37 C.F.R. § 1.21.

Dated: 7 July 1997

By: Arthur D. Gray by Arthur D. Gray
Arthur D. Gray (Reg. No. 26,170) by No. 34,045

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Atty. Docket No. 35467-61

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Zebedee et al.
Serial No. : 08/272,271
Filed : July 8, 1994
For : NON-A NON-B HEPATITIS VIRUS
ANTIGEN, DIAGNOSTIC METHOD
AND VACCINES
Examiner : D. C. Wortman
Art Unit : 1813

43/G
H.G.J.
7/21/97
(NE)

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JUL 21 1997

Assistant Commissioner
for Patents
Washington, D.C. 20231

GROUP 1630
I hereby certify that this AMENDMENT UNDER 37 C.F.R. § 1.116
is being deposited with the United States Postal Service as first class
mail in an envelope addressed to Assistant Commissioner for
Patents, Washington, D.C. 20231, on July 7, 1997.

Arthur D. Gray by M. J. Wille
Arthur D. Gray (Reg. No. 26,170) Lg No. 34045

AMENDMENT UNDER 37 C.F.R. § 1.116

Sir:

In response to the Office Action dated January
6, 1997, and in accordance with 37 C.F.R. § 1.116,
Applicants respectfully request entry of the present
amendment and remarks in the above-identified case.

IN THE CLAIMS:

In Claim 35, line 7, please delete "having the"
and insert therefore --consisting essentially of an--.

REMARKS

The Examiner has rejected claims 35 and 39-46
under 35 U.S.C. §103 as rendered obvious by Houghton et

Handwritten notes and signatures on the left margin.

al. (U.S. Patent No. 5,350,671; hereafter Houghton), in view of Smith et al. [Gene 67:31-40, (1988); hereafter Smith].¹

For the reasons stated herein, Applicants believe that the Examiner has failed to establish that Houghton and Smith render the present invention obvious. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Applicants' invention is directed to an immunoassay method for antibodies against non-A, non-B hepatitis virus (NANBV) using the particular antigenic, recombinant fusion protein identified by Applicants. To ensure that Applicants' invention is so-directed, Claim 35 has been amended to recite that the fusion protein has an amino acid sequence consisting essentially of the amino acid sequence as set forth in SEQ. ID NO. 4. Accordingly, from its N to C terminus, residues 1-120 of the fusion protein are the amino-terminal 120 residues of glutathione-S-transferase (GST), residues 221-226 are the cleavage site for the protease thrombin, and residues 227-246 are amino acid residues 21-40 of the NANBV capsid protein.

Both Houghton and Smith have been discussed on the record and general discussions thereof will not be

¹Applicants note that Claim 38 was previously cancelled and have responded to this rejection as if the Examiner intended the rejection to apply to Claims 35 and 39-46. The Examiner is invited to clarify this assumption if she believes it necessary.

repeated here. However, Applicants wish to draw the Examiner's attention to the discussion of the Smith reference set forth in the "Response" dated September 20, 1995, which is incorporated herein by reference.

At Page 3 of the instant Office Action, the Examiner stated that she has interpreted the discussion of the lengthy list of sequences (beginning at Col. 28, line 67) to mean that each and every one of 287 sequences listed contains an epitope. Applicants respectfully urge that the Examiner's interpretation on this point is in error for failing to have considered the teachings of Houghton as a whole.

The law is clear that the teachings of a reference must be taken as a whole for what they convey to one of ordinary skill in the art and that to read a passage of a reference in isolation is improper.

Houghton discloses at Col. 28, Lines 55-58, that the aforementioned list of HCV amino acid sequences may be useful in antigenic polypeptides. However, one of ordinary skill in the art, without more guidance, would view this isolated teaching as a wish list to identify useful epitopes and nothing more.

Houghton's further disclosure of the estimated sizes of epitopes, that non-immunogenic sequences can be identified and deleted, and that there are empirical methods such as the antigenic indices provided by hydrophilicity/hydrophobicity sequence plots or the use of short peptides to "scan" a longer sequence for the

presence of epitopes represents nothing more than a reiteration of general methods known in the art for finding and identifying epitopes. Locating useful antigens for immunoassay methods is an unpredictable and empirical task that mainly depends on the molecular framework of antigen presentation and the serum antibodies used. Thus, the list of sequences found in Houghton combined with a laundry list of methods to analyze such sequences does not provide the ordinarily skilled artisan with a reasonable expectation of success in locating any particular antigen, no less the antigenic fusion protein as claimed by Applicants.

But the above discussion does not represent the complete teachings of Houghton. To undertake the complete analysis of the teachings of Houghton needed to understand this reference as a whole, the ordinarily skilled artisan would ask whether Houghton has demonstrated if any of the listed sequences actually possessed useful antigenic activity for detection of antibodies against HCV. Indeed, Houghton does provide information in this regard beginning at Col. 81, Line 32 and continuing through Col. 83, Line 58, and particularly in the table entitled "Clones encoding polypeptides of proven reactivity with sera from NANBH patients" (Col. 83, Lines 34-54) wherein 17 individual fusion protein clones prepared from the 287 earlier-listed sequences are revealed as reactive to antibodies against NANBV. Houghton also presents the same information in graphic

and tabular form in Figs. 63 and 65, respectively. The data used to produce Fig. 63 appears to have been taken from Fig. 65 which sets forth the immunoreactivity of clones encoding a recombinant protein consisting of an SOD fusion to the indicated HCV amino acid sequence with a panel of NANBH patient sera. Fig. 63 thus illustrates the positional relationship on the HCV genome of clones with demonstrated immunogenicity to clones which lack such reactivity using sera from the same patients. Clearly, Fig. 63 establishes that Houghton was unable to demonstrate the existence of detectable HCV epitopes in extensive regions in the HCV genome. For example, no epitopes were disclosed in the regions represented by residues 177-437, by residues 690-1192 or by residues 2502-2796. Yet, many of the 287 suggested sequences interpreted by the Examiner as containing an epitope are completely within these demonstrably non-antigenic regions.

Moreover, a closer examination of the data in Fig. 65 indicates that many of the recombinant fusion proteins with "putative" proven reactivity to sera from NANBV patients react with only a few of the tested sera and are thus weak antigens and of unknown value in an immunoassay method to detect HCV antibodies.

Furthermore, the prediction of antigenicity based on hydrophilicity is significant to this discussion because Houghton touts it as a method to identify useful epitopes in the disclosed sequences. Yet, Houghton does

not consider this method to be more than a guide to the possible location of antigenic regions, and not necessarily a good guide at that: "It is appreciated by those of skill in the art that such computer analysis of antigenicity does not always identify an epitope that actually exists, and can also incorrectly identify a region of the protein as containing an epitope." (Col. 28, Lines 49-53).

Therefore, Houghton's data, his use of predictive methods and his own admissions further argue against the Examiner's assertion that each of the 287 listed sequences contains an epitope.

To summarize the teachings of Houghton as a whole from the perspective of the ordinarily skilled artisan, this reference teaches that a few recombinant fusion proteins with particular HCV amino acid sequences exhibit antigenicity to HCV antibodies. The fact that Houghton suggests additional means to locate other epitopes is nothing more than an invitation to experiment since, contrary to Houghton's assertion that epitopes can be found using the general methodology known in the art, identification of epitopes is an unpredictable process that does not carry a reasonable expectation of success. Hence, the Examiner's interpretation that each of the listed sequences contains an epitope is in error as demonstrated by Houghton's own data.

As pointed out in In re Fine, 5 U.S.P.Q.2d 1596, 1599 (Fed.Cir. 1988), one tests obviousness by what

the combined teachings of the references would have suggested to those of ordinary skill in the art. Obviousness cannot be established by combining teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. See, also, In re Jones, 21 U.S.P.Q.2d 1941, 1944 (Fed.Cir. 1992).

Here, the general methods disclosed by Houghton as applicable to locate epitopes in fact teaches away from Applicants' invention of a recombinant fusion protein of GST with HCV amino acid residues 21-40. For example, the antigenic index (see the hydrophilicity plot in Fig. 67) of the 21-40 HCV sequence predicts that there should not be an antigenic site located in this sequence. Houghton provides no further guidance that enables one of ordinary skill in the art to make and use a recombinant fusion of GST and the 21-40 HCV amino acid sequence. Smith generally teaches GST fusion proteins and their use to simplify purification of such fusion proteins together with cleavage of the GST portion from the fusion protein. Smith thus adds nothing with respect to identifying the 21-40 HCV sequence, either alone or as part of a fusion protein, for use as an antigen in an immunoassay method designed to detect NANBV antibodies.

This unpredictability is further evident from the experimental results related in Dr. Torsten Helting's declaration of October 12, 1993 and the discussion thereof as provided in the "Amendment under 37 C.F.R.

§1.116" dated October 12, 1993 in parent application U.S. Serial No. 07/616,369, which discussion is incorporated herein by reference. The data in Dr. Helting's declaration unequivocally show that the antigenicity of amino acid residues 21-40 depends upon whether that sequence is presented as a peptide or as part of a GST fusion protein. Dr. Helting established that a recombinant peptide corresponding to the HCV capsid sequence at positions 21-40 "shows an almost negligible level of activity ..." (Paragraph 17) under conditions where the fusion protein was active. Thus, a recombinant fusion protein construct as claimed in the present invention outperformed a peptide consisting of the 21-40 HCV sequence. That result was unexpected, not predicted and not obvious. It is also contrary to the teaching of Houghton.

In further support, Applicants cite In re Deuel, 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995) which held that the "fact that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious (emphasis in original)." Thus, the availability of generic techniques to identify a previously unidentified epitope does not render that epitope obvious. See also In re Baird, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994); In re Bell, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993); Bristol-Meyers Co. v. U.S.I.T.C., 15 U.S.P.Q.2d 1258 (Fed. Cir. 1989); In re

Kuehl, 475 F.2d 658 (Fed. Cir. 1973); In re Jones, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

In summing the teachings and facts of the references cited by the Examiner, (1) Houghton neither teaches nor suggests the use of a GST fusion protein containing the HCV peptide recited in the claims for use in an immunoassay; (2) the bare recombinant peptide is unexpectedly an ineffective antigen; (3) Houghton's disclosure of antigenic activity for fusion proteins consisting of SOD and HCV sequences different from those claimed teaches nothing regarding the antigenicity of the claimed fusion protein; (4) Smith's teaching of a GST-containing fusion protein to obtain enhanced purity makes no suggestion that such a fusion protein would also be useful as an antigen in an immunoassay for NANBV antibodies; and (5) Smith's complete teaching to make a GST-containing fusion protein, purify it and then cleave it to remove the GST portion here provides the useless, bare 21-40 peptide that does not work in such an assay.

In view of the foregoing amendments and remarks
it is firmly believed that the subject invention is in
condition for allowance, which action is earnestly
solicited. If the Examiner believes any matters remain
outstanding, she is invited to call the undersigned.

Respectfully submitted,

Dated: July 7, 1997

Arthur D. Gray by *Arthur D. Gray*
Arthur D. Gray
Reg. No. 26,170
Reg. No.
34,045

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New York, NY 10004

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08/272271



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/272,271	07/08/94	ZEBEDEE	5

18M1/0724
WELSH AND KATZ LTD
120 SOUTH RIVERSIDE PLAZA, 22ND FLOOR
CHICAGO IL 60606

EXAMINER	
WORTMAN, D	
ART UNIT	PAPER NUMBER
1815	44

DATE MAILED:

07/24/97

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☐ THE PERIOD FOR RESPONSE:

- a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection
- b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

- ☒ Appellant's Brief is due in accordance with 37 CFR 1.192(a).
- ☒ Applicant's response to the final rejection, filed 7/14/97 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☒ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:
- ☒ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
 - ☒ They raise new issues that would require further consideration and/or search. (See Note).
 - ☐ They raise the issue of new matter. (See Note).
 - ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
 - ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE:

see attached

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing of an appeal, the proposed amendment ☐ will be entered ☒ will not be entered and the status of the claims will be as follows:

Claims allowed: _____

Claims objected to: _____

Claims rejected: 35 and 39-46

However;

- ☐ Applicant's response has overcome the following rejection(s): _____

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because see attached

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other

Art Unit: 1815

The after final amendment to claim 35 will not be entered because it raises new issues under 35 USC 112, second paragraph, as it is unclear what "consisting essentially of" is intended to mean when it describes a fusion protein. "Consisting essentially of" has a conventionally understood meaning with respect to compositions. However, claim 35 is presently drawn to a method using a particular fusion protein that has the amino acid sequence given in SEQ ID NO:4. It is unclear what "consisting essentially of" is intended to encompass with respect to a particular amino acid sequence since it is not understood what else could be included in a recombinant NANBV fusion protein in addition to the recited SEQ ID NO. The proposed amendment would also raise a new issue under 35 USC 112, second paragraph, as to what applicants regard as their invention, since the Examiner has previously interpreted claim 35 as being drawn to a method using a recombinant NANBV fusion protein having the amino acid sequence given in SEQ ID NO:4. The proposed amendment reciting "consisting essentially of" suggests that the invention may be different from what was previously understood.

With respect to the rejection of record of claims 35 and 39-46 under 35 U.S.C. § 103(a) as being unpatentable over US patent 5,350,671 to Houghton et al. in view of Smith et al., applicant has urged that not all of the listed sequences Houghton at col. 28, line 67-col.29, line 68 were demonstrated to have antigenic activity, that some of recombinant fusion proteins tested had only weak reactivity with patient sera, that based on hydrophilicity the instant peptide would not have been predicted to have important epitopes, that Houghton does not provide further guidance that would enable one to make and use a recombinant fusion protein of GST and the 21-40 HCV amino acid sequence. In addition, applicant has referred to the Declaration of Dr. Helting, of record, and urged that the effectiveness of the claimed fusion protein compared with the relative ineffectiveness of the HCV 21-40 peptide, not in the form of a fusion protein, represents an unexpected result.

These arguments have been considered but not found persuasive. Considering the teachings of Houghton as a whole, and not just the portions of Houghton's disclosure that applicant has cited as not teaching applicant's invention, Houghton clearly demonstrates seroreactivity for AAl-84 (also represented by "CA279a" as shown in the table at col. 83), and provides the complete amino acid sequence for AAl-84, as well as suggesting appropriate sizes for shorter, epitope bearing peptides. No teachings regarding hydrophilicity and its value for predicting the location of antigenicity were relied upon. With respect to the Declaration of Dr. Helting, the activity of the fusion protein as compared to the 21-40 peptide apparently represents an improved result not over the prior art but rather over what is disclosed as an alternative (presently unclaimed) embodiment of applicant's own invention and thus is not persuasive of unobviousness over the prior art of record. Further, the specification does not disclose that the fusion protein provides better results in an immunoassay than the HCV 21-40

Serial Number: 08/272271

Page 3

Art Unit: 1815

peptide and thus the assertedly unexpected results are not supported by the specification. (MPEP 716.02(f); *In re Davies* 177 USPQ 381, 385).


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Wortman whose telephone number is (703) 308-1032. The examiner can normally be reached on Monday through Thursday from 7:30 am to 5:00 pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marian C. Knode

MARIAN C. KNODE
SUPERVISORY PATENT EXAMINER
GROUP 1800


Donna C. Wortman, Ph.D.
July 23, 1997

09/18/97

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BOX 44

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICESEP 22 1997
COMM-FIELD#45
C.G.
9/22/97

RC

REQUEST FOR EXTENSION OF TIME
PURSUANT TO 37 C.F.R. § 1.136(a)Docket Number:
55467/61Application Number
08/272,271Filing Date
July 8, 1994Examiner
D. WortmanArt Unit
1815Invention Title
NON-A, NON-B, HEPATITIS VIRUS ANTIGEN,
DIAGNOSTIC METHODS AND VACCINESInventor(s)
ZEBEDEE et al.Address to:
Assistant Commissioner for Patents
Washington D.C. 20231I hereby certify that this correspondence is being deposited with the
United States Postal Service as first class mail in an envelope addressed
to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

Date: September 16, 1997

Reg. No. 34,045

Signature:

M. Lisa Wilson

Applicant respectfully requests a one month extension of time in which to file a
response to the Notice of Appeal filed July 14, 1997, for which a response period expiring
on September 15, 1997 was set. The extended period expires on October 14, 1997.

1. The Commissioner is hereby authorized to charge payment of the 37 C.F.R. §
1.136(a) extension fee of \$110.00 to the deposit account of **Kenyon & Kenyon**,
deposit account number 11-0600. The Commissioner is also authorized to charge
any additional fees or credit any overpayment in connection with this paper to
Deposit Account No. 11-0600.
2. A duplicate copy of this form is enclosed.

Dated: September 16, 1997

By:

M. Lisa Wilson (Reg. No. 34,045)

09/19/1997 HVILLARI 00000118 DAW:110600 08272271
01 FC:115 110.00 CHKENYON & KENYON
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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
18/272,271	07/08/94	WELSH	

1841/0203
WELSH AND KATZ LTD.
120 SOUTH RIVERSIDE PLAZA, 22ND FLOOR
CHICAGO IL 60606

EXAMINER

ART UNIT

PAPER NUMBER

1815

DATE MAILED: 02/03/95

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

08/272 271



UNITED STATES DEPARTMENT OF COMMERCE

Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT PAPER NUMBER

DATE MAILED:

NOTIFICATION OF DEFECTIVE NOTICE OF APPEAL OR DEFECTIVE BRIEF

1. ☐ The Notice of Appeal filed _____ is:A. ☐ Not acceptable for reason(s) that:

- (1) ☐ The Appeal fee required by 35 U.S.C. 41 (a)(6) and 37 CFR 1.17(e) was not submitted with the Notice of Appeal.
- (2) ☐ The submitted fee of \$ _____ is insufficient. The appeal fee per 37 CFR 1.17(e) is \$ _____.
- (3) ☐ The Appeal was not timely filed.
- (4) ☐ The Appeal fee received on _____ was not timely filed.
- (5) ☐ The Appeal is not in compliance with 37 CFR 1.191 in that there is no record of a second or a final rejection in this application.
- (6) ☐ A letter of allowability was mailed by the Office on _____.

B. ☐ Defective and should be corrected as indicated. Applicant is given a TIME LIMIT of ONE MONTH from the date of this letter OR the TIME REMAINING IN THE RESPONSE PERIOD OF THE LAST OFFICE ACTION, whichever is longer, to complete the appeal. NO EXTENSION OF THIS TIME LIMIT MAY BE GRANTED UNDER EITHER 37 CFR 1.136(a) or (b) BUT THE PERIOD FOR RESPONSE SET IN THE LAST ACTION MAY POSSIBLY BE EXTENDED. If the appeal is not timely completed, the application will be abandoned as of the date of expiration of the period for response of the last Office action.

- (1) ☐ Unsigned. A ratification properly signed, is required.
- (2) ☐ Identification of the appealed claim or claims is required under 37 CFR 1.191 (b).

2. ☐ The Brief filed _____ is NOT acceptable for the reason(s) indicated below.

The Appeal in this application will be dismissed unless the applicant makes the Brief acceptable. Extensions of time may be obtained under 37 CFR 1.136(a).

- A. ☐ The Brief and/or Brief fee is untimely. See 37 CFR 1.192.
- B. ☐ The requisite fee which must accompany the Brief has been omitted. See 37 CFR 1.17(f).
- C. ☐ The submitted Brief fee of _____ is not the proper amount. The Brief fee per 37 CFR 1.17(f) is _____.

3. ☒ The Appeal in this application is DISMISSED because:

- A. ☐ The fee for filing the Brief as required under 37 CFR 1.17(f) was not submitted or timely submitted and the period for obtaining an extension of time to file the brief under 37 CFR 1.136 has expired.
- B. ☒ The Brief was not filed, or was not timely filed and the period for obtaining an extension of time to file the brief under 37 CFR 1.136 has expired.

4. ☒ As the result of the dismissal in 3. above, this application:

- A. ☒ is abandoned since there are no allowed claims.
- B. ☐ is being returned to the examiner for disposition since it contains allowed claims. Prosecution on the merits is CLOSED.

MARIAN C. KNOPE
SUPERVISORY PATENT EXAMINER
GROUP 1800

REQUEST FOR ACCESS TO AN ABANDONED APPLICATION UNDER 37 CFR 1.14

Bring completed form to:
File Information Unit
Crystal Plaza Three, Room 1001
2021 South Clark Place
Arlington, VA
Telephone: (703) 306-2733

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FEB 03 2006

File Information Unit

In re Application of

Application Number

08/272,271

Filed

7-8-94

Page No.

#47

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page _____, line _____

United States Patent Number 6692751, column _____, line _____, or

WIPO Pub. No. _____, page _____, line _____

Related Information about Access to Pending Applications (37 CFR 1.14):

Direct access to pending applications is not available to the public but copies may be available and may be purchased from the Office of Public Records upon payment of the appropriate fee (37 CFR 1.19(b)), as follows:
For published applications that are still pending, a member of the public may obtain a copy of:

- the file contents;
- the pending application as originally filed; or
- any document in the file of the pending application.

For unpublished applications that are still pending:

- (1) If the benefit of the pending application is claimed under 35 U.S.C. 118(e), 120, 121, or 365 in another application that has: (a) issued as a U.S. patent, or (b) published as a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:

- the file contents;
- the pending application as originally filed; or
- any document in the file of the pending application.

- (2) If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
the pending application as originally filed.

Henry Duong

Signature

HENRY DUONG

Typed or printed name

Registration Number, if applicable

703 916 1500

Telephone Number

2-3-06

Date

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Approved by: *[Signature]*

FEB 03 2006

Unit: File Information Unit

E.T.U.

6/63/9

> O <
OI IO IntelliGenetics
> O <

FastDB - Fast Pairwise Comparison of Sequences
Release 5.4

Results file wortman-616-fig1-a-geneseq.res made by maryh on Wed 25 Mar 92
17033:05-PST.

Query sequence being compared: WORTMAN-616-FIG1 (1-240)
Number of sequences searched: 14140
Number of scores above cutoff: 3918

Results of the initial comparison of WORTMAN-616-FIG1 (1-240) with:
Data bank : A-GeneSeq 5, all entries

10000-
--
N -- *
U 5000-
M --
B25 --
E *
R -- ** *
O --
F30000-
--
S -- *
E 500-
Q --
U35 --
E --
N --
C --
E --* *
S40100-
--
50- *
45 --
--
50 10-
-- *
5-
--

3. R12600 PT-NANBH viral structural and 603 30 30 20.72

1
 1 4. R13343 **** 19 standard deviations above mean ****
 P1 HCV antigen (1-75). 75 36 36 19.57
 1 5. R11274 Hepatitis C virus J7 isolate 154 36 36 19.57
 1 6. R08124 Hepatitis C virus putative po 2955 36 36 19.57
 1 5
 1 7. R12596 **** 16 standard deviations above mean ****
 Antigenic portion of PT-NANB 278 30 30 16.11
 1
 1 8. P81758 **** 4 standard deviations above mean ****
 Sequence encoded by env gene 735 10 12 4.60
 1
 1 9. P80805 Sequence of env protein of SI 880 10 12 4.60
 1 10
 1 10. R12345 Toxoplasma gondii protein fra 392 9 10 4.03
 1
 1 11. R12352 Toxoplasma gondii P66 antigen 428 9 10 4.03
 1
 1 12. R08034 Unique sequence fragment of H 486 9 9 4.03
 1
 1 13. P80803 Sequence of env protein of HI 856 9 10 4.03
 1
 1 14. P80806 Sequence of env protein of HI 858 9 11 4.03
 1 15
 1 15. P81779 Sequence encoded by open read 858 9 11 4.03
 1
 1 16. P82677 ENVRN sequence from HIV-2 ROD 891 9 11 4.03
 1
 1 17. R04196 **** 3 standard deviations above mean ****
 Art gene of simian immunodeficiency 83 8 11 3.45
 1
 1 18. R10846 Hepatitis C virus antigen enc 160 8 10 3.45
 1 20
 1 19. P92023 Sequence encoded in the hepat 160 8 10 3.45
 1
 1 20. P90140 Protein sequence of hepatitis 160 8 10 3.45
 1

Query sequence being compared: WORTMAN-616-FIG1 (1-240)
 Number of sequences optimized: 3918

Results of the optimized comparison of WORTMAN-616-FIG1 (1-240) with:
 Data bank : A-GeneSeq 5, all entries

30

PARAMETERS

Similarity matrix	Unitary	K-tuple	2
Translation Frame	1		

Mismatch penalty	1	Joining penalty	20
Gap penalty	1.00	Window size	32
Gap size penalty	0.05		
Cutoff score	2		
Randomization group	0		
40			
Initial scores to save	20	Alignments to save	10
Optimized scores to save	20	Display context	10

SEARCH STATISTICS

45			
Scores:	Mean	Median	Standard Deviation
	8	10	0.92
Times:	CPU		Total Elapsed
50	00:01:02.09		00:02:08.00
Number of residues:		1536423	
Number of sequences optimized:		3918	

The scores below are sorted by optimized score.
Significance is calculated based on optimized score.

A 100% identical sequence to the query sequence was not found.

5

The list of best scores is:

me	Sequence Name	Description	Length	Init.	Opt.	Sig.	Fra
				Score	Score		
10							

		**** 32 standard deviations above mean ****					
1	1. R12597	PT-NANB viral structural prot	66	38	38	32.70	
1	2. R13558	HCV core protein immunodominant	119	38	38	32.70	
1	3. R12600	PT-NANBH viral structural and	603	38	38	32.70	
15							
		**** 30 standard deviations above mean ****					
1	4. R13343	P1 HCV antigen (1-75).	75	36	36	30.52	
1	5. R11274	Hepatitis C virus J7 isolate	154	36	36	30.52	
1	6. R08124	Hepatitis C virus putative po	2955	36	36	30.52	
20							
		**** 23 standard deviations above mean ****					
1	7. R12596	Antigenic portion of PT-NANB	278	30	30	23.98	
		**** 6 standard deviations above mean ****					
1	8. P81013	Complete sequence of the pseu	479	6	14	6.54	
1	9. R13049	CD4-specific CDR-grafted heav	464	6	14	6.54	
25							
		**** 5 standard deviations above mean ****					
1	10. P70277	Sequence of pre-pro-insulin-1	195	5	13	5.45	
		**** 4 standard deviations above mean ****					
1	11. P60042	Sequence encoded by the leade	77	5	12	4.36	
1	12. P70323	Sequence encoded by 5' sequen	77	5	12	4.36	
1	13. R07049	Alkaline phosphatase C-termin	77	5	12	4.36	
30							
1	14. R08257	B.thuringiensis toxin gene pr	1174	6	12	4.36	
1	15. P81758	Sequence encoded by env gene	735	10	12	4.36	
1	16. P80805	Sequence of env protein of SI	880	10	12	4.36	
1	17. R05427	Circumsporozoite (CS)-related	559	4	12	4.36	
1	18. P80927	Sequence of the human mineral	984	5	12	4.36	
35							
1	19. R06893	Tilapia prolactin I.	212	5	12	4.36	
1	20. P80291	Interleukin-24InE.Fc fusion p	367	5	12	4.36	

140WORTMAN-616-FIG1 (1-240)

R12597 PT-NANB viral structural protein encoded by clone

ID R12597 standard; Protein; 66 AA.
AC R12597;
DS 06-SEP-1991 (first entry).
DE PT-NANB viral structural protein encoded by clone 164/137.
KW post-transfusional non-A, non-B hepatitis; virus; vaccine.
OS Non-A, non-B hepatitis virus.
PN GB2239245-A.
BD 26-JUN-1991.
PF 17-DEC-1990; 027250.
PR 18-DEC-1989; GB-028562.
PR 27-FEB-1990; GB-004414.
PR 03-MAR-1990; GB-004814.

PR 17-DEC-1990; GB-027250.
 PA (WELL) WELLCOME FOUNDATION LTD.
 PI Highfield PE, Rodgers BC, Tedder RS, Barbara JAJ;
 DR WPI; 91-187584/26.
 DN N-PSDB; Q12237.
 PT Post-transfusional non-A non-B hepatitis poly:peptide(s) -- and
 PT also DNA and antibodies used in diagnostic assays and in vaccines
 PS Claim 1; Page 71-72; 108pp; English.
 CC The sequence was deduced from a structural coding region sequence
 CC isolated from serum of humans infected by the PT-NANBH virus.
 CC The polypeptide is an antigenic portion of the virus and will be
 CC useful in the development of vaccines for inducing immunity in man to
 CC PT-NANBH. The invention covers PT-NANBH viral polypeptides having
 CC an amino acid sequence at least 90 per cent homologous with the
 CC sequence given here, or antigenic fragments of such homologous
 CC sequences.
 CC See also Q12236-8 and Q12240-Q12242.
 SQ Sequence 66 AA;
 SQ 1 A; 13 R; 3 N; 1 D; 0 B; 0 C; 5 Q; 1 E; 0 Z; 8 G; 0 H;
 SQ 2 I; 3 L; 5 K; 1 M; 1 F; 9 P; 3 S; 5 T; 0 W; 1 Y; 4 V;

Initial Score = 38 Optimized Score = 38 Significance = 32.70
 Residue Identity = 97% Matches = 38 Mismatches = 1
 Gaps = 0 Conservative Substitutions = 0
 Translation Frame= 1

X 10 20 30 X
 STIPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
 || |||||
 30 MSTNPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATR
 X 10 20 30 40 50

2. WORTMAN-616-FIG1 (1-240)

35R13558 HCV core protein immunodominant region.

ID R13558 standard; Protein; 119 AA.
 AC R13558;
 DT 28-OCT-1991 (first entry)
 DD HCV core protein immunodominant region.
 KW Hepatitis C virus; non-A non-B hepatitis virus; diagnosis;
 KW C-100 protein; core protein; vaccines; NANBHV.
 OS Synthetic.
 FH Key Location/Qualifiers
 #S Peptide 1..61
 FT /label= VIIIE
 FT Peptide 59..119
 FT /label= IXE
 PN EP-442394-A.
 BD 21-AUG-1991.
 PF 08-FEB-1991; 101787.
 PR 16-FEB-1990; US-481348.
 PR 16-APR-1990; US-510153.
 PR 26-JUL-1990; US-558799.

PA (UNBI-) UNITED BIOMED INC.
 PI Wang CY;
 DR WPI; 91-247104/34.
 PT New synthetic peptide(s) from immuno-dominant regions of virus -
 PS for diagnosis of hepatitis C virus and non -A, -B hepatitis
 PT infection, esp. using enzyme-linked immuno-sorbent assay
 PS Disclosure; Page 16; 93pp; English.
 CC In selecting regions of the HCV protein for epitope analysis,
 CC peptides in the 40 mer size range with amino acid sequences covering
 CC the complete HCV C-100 protein and the core protein were synthesised.
 CC These were tested for their reactivity with serum from a patient
 CC positively diagnosed with HCV infection. The indicated
 CC two overlapping peptides from the HCV core protein region
 CC were found to have specific immunoreactivity with the positive
 CC control serum. The peptides may be used in highly sensitive and
 CC accurate methods for the early detection of antibodies to HCV in
 CC body fluids and the diagnosis of NANBHV infection. Because of
 CC their high immunoreactivity, the peptides are also useful in
 CC stimulating prodn. of antibodies to HCV and in vaccines to prevent
 CC HCV or NANBHV infection.
 CC See also R13557 for C-100 protein immunodominant peptides.
 SQ Sequence 119 AA;
 SQ 3 A; 22 R; 4 N; 2 D; 0 B; 1 C; 7 Q; 3 E; 0 Z; 16 G; 0 H;
 SQ 3 I; 7 L; 6 K; 0 M; 1 F; 17 P; 7 S; 7 T; 5 W; 3 Y; 5 V;
 25
 Initial Score = 38 Optimized Score = 38 Significance = 32.70
 Residue Identity = 97% Matches = 38 Mismatches = 1
 Gaps = 0 Conservative Substitutions = 0
 Translation Frame= 1

30
 X 10 20 30 X
 STIPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
 |||||
 STIPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATR
 35 X 10 20 30 40

3. WORTMAN-616-FIG1 (1-240)
 R12600 PT-NANBH viral structural and non-structural prote
 40
 ID R12600 standard; Protein; 603 AA.
 AC R12600;
 DT 17-SEP-1991 (first entry)
 DE PT-NANBH viral structural and non-structural proteins.
 K0 post-transfusional non-A, non-B hepatitis; virus; vaccine; ss.
 OS Non-A, non-B hepatitis virus.
 PN GB2239245-A.
 PD 26-JUN-1991.
 PF 17-DEC-1990; 027250.
 BB 18-DEC-1989; GB-020562.
 PR 27-FEB-1990; GB-004414.
 PR 03-MAR-1990; GB-004814.
 PR 17-DEC-1990; GB-027250.
 PA (WELL) WELLCOME FOUNDATION LTD.

PI Highfield PE, Rodgers BC, Tedder RG, Barbara JAJ;
 DR WPI; 91-187584/26.
 DR N-PSDB; Q12242.
 PT Post-transfusional non-A non-B hepatitis poly:peptide(s) - and
 PF also DNA and antibodies used in diagnostic assays and in vaccines
 PS Claim 1; Page 83-87; 108pp; English.
 CC The sequence was deduced from a "structural/non-structural" coding
 CC region sequence isolated from serum of humans infected by the
 CC PT-NANBH virus. The polypeptide is an antigenic portion of the virus
 CC and will be useful in the development of vaccines for inducing
 CC immunity in man to PT-NANBH. The invention covers PT-NANBH viral
 CC polypeptides having an amino acid sequence at least 90 per cent
 CC homologous with the sequence given here, or antigenic fragments of
 CC such homologous sequences.
 CC See also Q12236-41.
 SQ Sequence 603 AA;
 SQ 47 A; 42 R; 30 N; 21 D; 0 B; 24 C; 20 Q; 13 E; 0 Z; 66 G; 15 H;
 SQ 20 I; 48 L; 12 K; 15 M; 19 F; 49 P; 37 S; 45 T; 17 W; 20 Y; 43 V;

Initial Score = 38 Optimized Score = 38 Significance = 32.70
 Residue Identity = 97% Matches = 38 Mismatches = 1
 Gaps = 0 Conservative Substitutions = 0
 Translation Frame= 1

25 X 10 20 30 X
 STIPKPKQRKTKRNTNRRFQDVKFPGGGQIVGGVYLLPRR
 || |||||
 MSTNPKPKQRKTKRNTNRRFQDVKFPGGGQIVGGVYLLPRRGPTLGVRATR
 X 10 20 30 40 50
 30

4. WORTMAN-616-FIG1 (1-240)
 R13343 P1 HCV antigen (1-75).

JB R13343 standard; Protein; 75 AA.
 AC R13343;
 DT 23-OCT-1991 (first entry)
 DE P1 HCV antigen (1-75).
 KW C100-3; hepatitis C virus; immunoassay; epitope.
 QQ Synthetic.
 PN AU9068390-A.
 QD 27-JUN-1991.
 PF 21-DEC-1990; 068390.
 PR 22-DEC-1989; US-456162.
 RB 07-NOV-1990; US-610180.
 PA (ABBO) ABBOTT LABORATORIES.
 DR WPI; 91-238393/33.
 DR N-PSDB; Q13146.
 PT Immunological assays for hepatitis C virus antibody - by using
 BQ polypeptide(s) contg. epitope(s) of hepatitis C virus antigens
 PS Claim 10; Page 48; 62pp; English.
 CC The polypeptide may be prepared by solid phase synthesis fragment
 CC coupling or using recombinant technology.
 CC The assay has increased sensitivity and is more specific than

CC assays using the polypeptide C100-3 (EP-318216).
 CC See also Q13146-48 and R13343-65.
 SQ Sequence 75 AA;
 SQ 2 A; 15 R; 4 N; 1 D; 0 B; 0 C; 5 Q; 2 E; 0 Z; 9 G; 0 H;
 SQ 2 I; 3 L; 7 K; 1 M; 1 F; 10 P; 3 S; 5 T; 0 W; 1 Y; 4 V;

Initial Score = 36 Optimized Score = 36 Significance = 30.52
 Residue Identity = 92% Matches = 36 Mismatches = 3
 Gaps = 0 Conservative Substitutions = 0
 Translation Frame = 1

```

      X      10      20      30      X
      STIPKPKQKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
      || ||||| | ||||| | ||||| | ||||| | ||||| |
15 MSTNPKPKQKKNKRNTRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATR
      X      10      20      30      40      50

```

5. WORTMAN-616-FIG1 (1-240)

20R11274 Hepatitis C virus J7 isolate C/E domain polypeptid

ID R11274 standard; Protein; 154 AA.
 AC R11274;
 DT 30-MAY-1991 (first entry)
 BE Hepatitis C virus J7 isolate C/E domain polypeptide prod.
 KW Hepatitis C virus; HCV-J1; HCV-J7; vaccines; NANBH.
 OS Hepatitis C virus.
 FH Key Location/Qualifiers
 FT Misc_difference 8..8
 EQ /label= Gln, Arg
 FT Misc_difference 25..25
 FT /label= Pro, Leu
 FT Misc_difference 91..91
 FT /label= Leu, OTHER
 EQ /note= "OTHER= termination of sequence"
 FT Misc_difference 110..110
 FT /label= Asn, Thr
 FT Misc_difference 130..130
 FT /label= Phe, Leu
 EQ EP-419182-A.
 PD 27-MAR-1991.
 PF 17-SEP-1990; 310149.
 PR 15-SEP-1989; US-408045.
 PR 21-DEC-1989; US-456142.
 AB (CHIR-) CHIRON CORP.
 PI Miyamura T, Saito T, Houghton M, Weiner AJ, Han J;
 PI Kolberg JA, Chata T-A, Irvine BD;
 DR WPI; 91-088781/13.
 DR N-PSDB; Q11075.
 EQ New isolates J1 and J7 of hepatitis C virus - contg. specified
 PT DNA and amino acid sequences, used in diagnosis, recombinant
 PT protein prodn. and vaccine
 PS Disclosure; fig 1; 109pp; English.
 CC This polypeptide prod. is encoded by a fragment of the hepatitis

FT Misc_difference 1471..1471
 FT /label=T or S
 FT Misc_difference 1877..1877
 FT /label=E or G
 FT Misc_difference 1948..1948
 FT /label=L or H
 FT Misc_difference 1949..1949
 FT /label=S or C
 FT Misc_difference 2021..2021
 FT /label=V or G
 FT Misc_difference 2349..2349
 FT /label=T or S
 FT Misc_difference 2385..2385
 FT /label=Y or F
 FT Misc_difference 2386..2386
 FT /label=S or A
 FT Misc_difference 2502..2502
 FT /label=L or F
 FT Misc_difference 2690..2690
 FT /label=R or G
 FT Misc_difference 2921..2921
 FT /label=R or G
 PN EP-388232-A.
 PD 19-SEP-1990.
 BS 16-MAR-1990; 302866.
 PR 17-MAR-1989; US-325338.
 PR 20-APR-1989; US-341334.
 PR 18-MAY-1989; US-355002.
 PA (CHIR-) CHIRON CORP.
 BO Houghton M, Choo QL, Kuo G;.
 DR WPI; 90-284418/38.
 DR N-PDB; Q05956.
 PT Hepatitis C virus DNA - used for producing probes,
 PT polypeptide(s), antibodies and anti-sense polynucleotide(s) for
 BS diagnosis and therapy.
 PS Disclosure; Fig 17; 83pp; English.
 CC HCV cDNA libraries were constructed using pooled serum from a
 CC chimpanzee with chronic HCV infection. A lambda gt11 library was
 CC screened with probes derived from previously isolated clones. The
 BO ORF is derived from the overlapping clones b114a, ag30a, CA205a,
 CC CA290a, CA216a, pi4a, CA167b, CA156e, CA84a, CA59a, K9-1, 26j, 13i,
 CC 12f, 14i, 11b, 7f, 8h, 33c, 40b, 37b, 35, 36, 81, 32, 33b, 25c,
 CC 14c, 8f, 33f, 33g, 39c, 35f, 19g, 26g, 15e, b5a and 16jh.
 CC Polypeptide encoded by this sequence can be used to design probes
 BS for the detection of HCV nucleic acids, in screening programmes
 CC for antiviral agents and in preparing blood free of HCV. The
 CC sequence contains 186 (overlapping) peptides which are claimed as
 CC HCV epitopes.
 CC See also Q05955.
 SO Sequence 2955 AA;
 SO 270A; 168R; 86 N; 119D; 0 B; 101C; 89 Q; 114E; 0 Z; 246G; 68 H;
 SO 127I; 295L; 95 K; 54 M; 84 F; 205P; 201S; 214T; 68 W; 94 Y; 236V;
 SO 21 Others;

10 20 30 X
STIPKPRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
||||| ||||| ||||| ||||| |||||
RKTNRNTNLRPQDVRFPGGGQIVGGVYLLPRRGPRLGVRATR
5 X 10 20 30 X 40

10

15

20

25

30

35

40

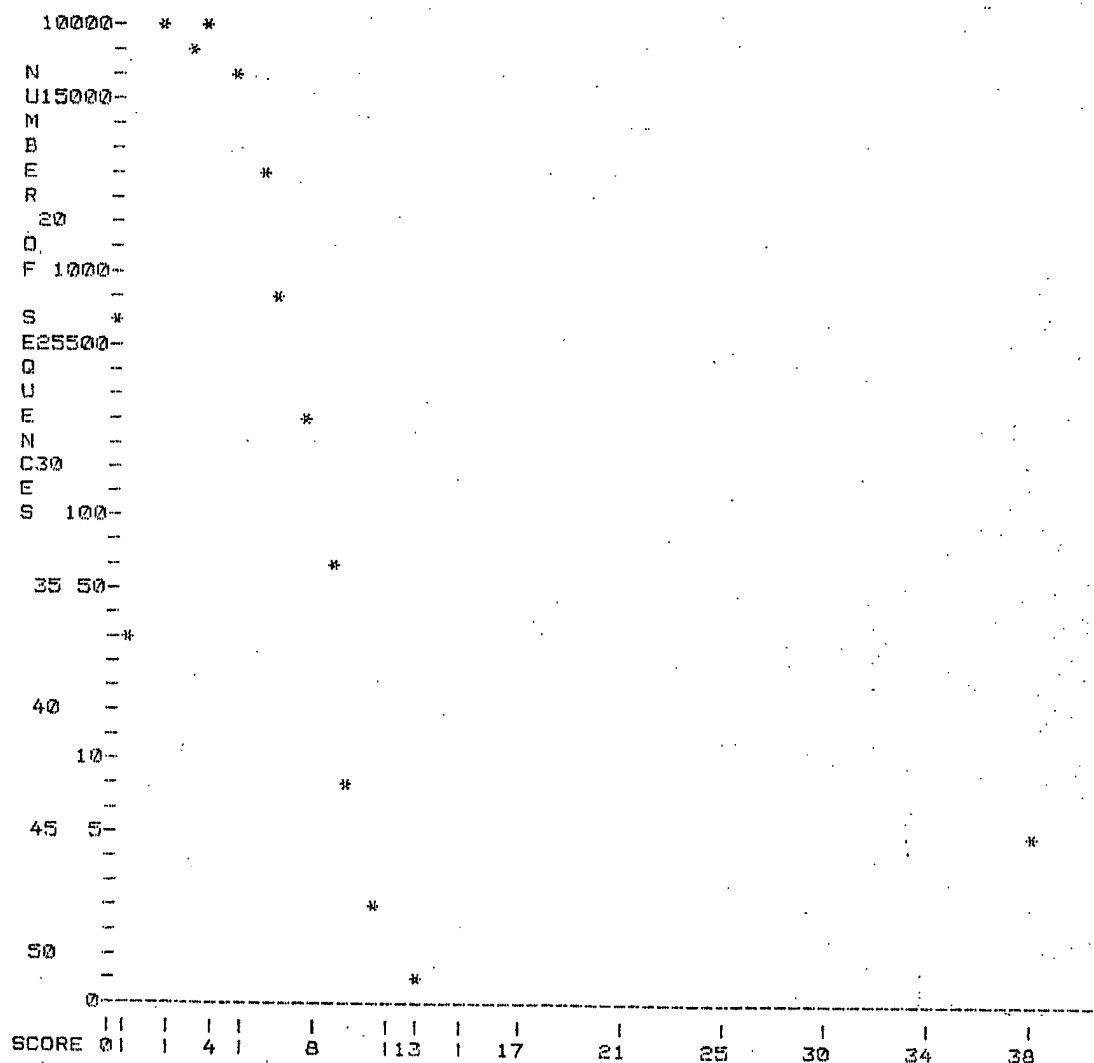
45

50

Results file wortman-616-fig1-pir.res made by maryh on Wed 25 Mar 92
17:35:35-PST.

Query sequence being compared: WORTMAN-616-FIG1 (1-240)
Number of sequences searched: 33989
Number of scores above cutoff: 3927

Results of the initial comparison of WORTMAN-616-FIG1 (1-240) with:
10Data bank : PIR 30, all entries



STDEV -1 0 2 4 6 8

PARAMETERS

5
Similarity matrix Unitary K-tuple 2
Translation Frame 1
Mismatch penalty 1 Joining penalty 20
Gap penalty 1.00 Window size 32
Gap size penalty 0.05
Cutoff score 2
Randomization group 0

Initial scores to save 20 Alignments to save 10
Optimized scores to save 20 Display context 10

SEARCH STATISTICS

Scores: Mean Median Standard Deviation
20 3 5 1.48

Times: CPU Total Elapsed
00:01:47.13 00:03:30.00

Number of residues: 9697617
Number of sequences searched: 33989
Number of scores above cutoff: 3927

Cut-off raised to 3.
Cut-off raised to 4.
Cut-off raised to 5.
Cut-off raised to 6.
Cut-off raised to 7.

TSB scores below are sorted by initial score.
Significance is calculated based on initial score.

A 100% identical sequence to the query sequence was not found.

40
The list of best scores is:

Sequence Name	Description	Length	Init. Score	Opt. Score	Sig. Fra
**** 23 standard deviations above mean ****					
1. S12707	*Polyprotein - Hepatitis C vi	441	38	38	23.68
2. JQ0883	*Genome polyprotein - Hepatit	874	38	38	23.68
3. JQ0881	*Genome polyprotein - Hepatit	874	38	38	23.68
4. A38465	*Genome polyprotein - Hepatit	3010	38	38	23.68
**** 6 standard deviations above mean ****					
5. A20209	*Genome polyprotein - Hepatit	542	13	16	7.77

1

6. S14145

1

**** standard deviations above mean ****
*Depressed growth-rate protei 2 11 12 5.41

7. MMECHP	Hexose phosphate transport pr	463	11	12	5.41
-----------	-------------------------------	-----	----	----	------

*** 4 standard deviations above mean ***

#Arylesterase precursor - Pse	236	10	12	4.74
-------------------------------	-----	----	----	------

*Fumarate reductase flavoprot	256	10	11	4.74
-------------------------------	-----	----	----	------

Early E1A protein - Human ade	261	10	10	4.74
-------------------------------	-----	----	----	------

Helix-destabilizing protein -	365	10	11	4.74
-------------------------------	-----	----	----	------

Gene ND1 intron 3 protein 2 -	580	10	11	4.74
-------------------------------	-----	----	----	------

env polyprotein - Simian immu	881	10	12	4.74
-------------------------------	-----	----	----	------

Host specificity protein J -	1132	10	12	4.74
------------------------------	------	----	----	------

Histone H2B.1, sperm - Sea ur	144	9	13	4.06
-------------------------------	-----	---	----	------

Tandem-repeated DNA-binding p	161	9	11	4.06
-------------------------------	-----	---	----	------

*Hypothetical protein - Human	162	9	10	4.06
-------------------------------	-----	---	----	------

Nonstructural protein C - Can	174	9	11	4.06
-------------------------------	-----	---	----	------

Female-specific transformer p	197	9	12	4.06
-------------------------------	-----	---	----	------

Complement component C8 gamma	202	9	11	4.06
-------------------------------	-----	---	----	------

Query sequence being compared:WORTMAN-616-FIG1 (1-240)

Number of sequences optimized: 3927

220 Results of the optimized comparison of WORTMAN-616-FIG1 (1-240) with:
Data bank : PIR 30, all entries

PARAMETERS

25			
Similarity matrix	Unitary	K-tuple	0
Translation Frame	1		
Mismatch penalty	1	Joining penalty	20
Gap penalty	1.00	Window size	32
GAP size penalty	0.05		
Cutoff score	2		
Randomization group	0		
Initial scores to save	20	Alignments to save	10
Optimized scores to save	20	Display context	10

SEARCH STATISTICS

Scores: Mean Median Standard Deviation
 9 11 0.

Times: CPU Total Elapsed
 00:01:27.08 00:04:13.00

Number of residues: 1813548
Number of sequences optimized: 3927

The scores below are sorted by optimized score.
Significance is calculated based on optimized score.

A 100% identical sequence to the query sequence was not found.

The list of best scores is:

me	Sequence Name	Description	Init. Opt.		Sig. Fra
			Length	Score	
5		**** 30 standard deviations above mean ****			
1	1. S12707	*Polyprotein - Hepatitis C vi	441	38	38 30.99
1	2. J00883	*Genome polyprotein - Hepatit	874	38	38 30.99
1	3. J00881	*Genome polyprotein - Hepatit	874	38	38 30.99
1	4. A38465	*Genome polyprotein - Hepatit	3010	38	38 30.99
10		**** 7 standard deviations above mean ****			
1	5. A29209	60K filarial antigen - Nemato	548	13	16 7.40
		**** 5 standard deviations above mean ****			
1	6. VGBEP8	Glycoprotein gIII precursor -	479	6	14 5.34
15		**** 4 standard deviations above mean ****			
1	7. A39046	*Tissue factor precursor - Mo	294	6	13 4.28
1	8. DESH6C	Phosphogluconate dehydrogenas	466	7	13 4.28
1	9. VVVP24	Coat protein VP2 - Rhesus mac	352	5	13 4.28
1	10. IGHI1B	Insulin-like growth factor IB	195	5	13 4.28
1	11. WZBE6	Gene 6 protein - Varicella-zo	1083	6	13 4.28
20					
1	12. XYPS7A	Site-specific methyltransfera	531	6	13 4.28
1	13. R5ZPD4	Ribosomal protein KD4 - Yeast	253	7	13 4.28
1	14. R3FP12	Ribosomal protein S12 - Param	139	7	13 4.28
1	15. H5UR2P	Histone H2B.1, sperm - Sea ur	144	9	13 4.28
1	16. EDBE1F	Immediate-early protein IE180	1460	8	13 4.28
25					
1	17. A29514	Muscarinic acetylcholine rece	460	6	13 4.28
1	18. G3MSM	Ig gamma-3 chain C region, me	398	6	13 4.28
1	19. S10226	*Elongation factor 1-alpha -	454	9	13 4.28
1	20. G3MSC	Ig gamma-3 chain C region, se	329	6	13 4.28
30					
	1. WORTMAN-616-FIG1 (1-240)				
	S12707	*Polyprotein - Hepatitis C virus			
	ENTRY	S12707	#Type Protein		
	TITLE	*Polyprotein - Hepatitis C virus			

DATE 10-Jul-1991 #Sequence 10-Jul-1991 #Text 10-Jul-1991
 PLACEMENT 0.0 0.0 0.0 0.0 0.0
 COMMENT *This entry is not verified.
 SOURCE hepatitis C virus
 REFERENCE
 #Authors Takeuchi K., Kubo Y., Boonmar S., Watanabe Y.,
 Katayama T., Choo Q.L., Kuo G., Houghton M., Saito
 I., Miyamura T.
 #Journal Nucleic Acids Res. (1990) 18:4626
 #Title Nucleotide sequence of core and envelope genes of
 the hepatitis C virus genome derived directly from
 human healthy carriers.
 #Reference-number S12707
 #Accession S12707
 SUMMARY #Molecular-weight 47075 #Length 441 #Checksum 1573
 SEQUENCE

Initial Score = 38 Optimized Score = 38 Significance = 30.99

Residue Identity = 97% Matches = 38 Mismatches = 1
 Gaps = 0 Conservative Substitutions = 0
 Translation Frame= 1

```

5  X      10      20      30      X
   STIPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
   || |||||
   MSTNPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATR
   X      10      20      30      40      50
10

```

2. WORTMAN-616-FIG1 (1-240)

JQ0883 *Genome polyprotein - Hepatitis C virus isolate J7

ENTRY JQ0883 #Type Protein (fragment)
 TITLE *Genome polyprotein - Hepatitis C virus isolate J7
 (fragment)
 DATE 14-Apr-1991 #Sequence 14-Apr-1991 #Text 14-Apr-1991
 PLACEMENT 0.0 0.0 0.0 0.0 0.0
 COMMENT *This entry is not verified.
 SOURCE hepatitis C virus
 REFERENCE
 #Authors Okamoto H.
 #Citation submitted to JIPID, January 1991
 25 #Reference-number JQ0883
 #Accession JQ0883
 SUMMARY #Length 874 #Checksum 2054
 SEQUENCE

Initial Score = 38 Optimized Score = 38 Significance = 30.99
 Residue Identity = 97% Matches = 38 Mismatches = 1
 Gaps = 0 Conservative Substitutions = 0
 Translation Frame= 1

```

35 X      10      20      30      X
   STIPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
   || |||||
   MSTNPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATR
   X      10      20      30      40      50
40

```

3. WORTMAN-616-FIG1 (1-240)

JQ0881 *Genome polyprotein - Hepatitis C virus isolate J6

ENTRY JQ0881 #Type Protein (fragment)
 TITLE *Genome polyprotein - Hepatitis C virus isolate J6
 (fragment)
 DATE 14-Apr-1991 #Sequence 14-Apr-1991 #Text 14-Apr-1991
 PLACEMENT 0.0 0.0 0.0 0.0 0.0
 COMMENT *This entry is not verified.
 SOURCE hepatitis C virus
 REFERENCE
 #Authors Okamoto H.
 #Citation submitted to JIPID, January 1991

#Accession J00881

#Length 874 #Checksum 4519

5

```
Initial Score      =      38  Optimized Score =      38  Significance = 30.99
Residue Identity  =     97%  Matches          =      38  Mismatches   =      1
Gaps              =       0  Conservative Substitutions =      0
Translation Frame =       1
```

17

```

X           10           20           30           X
STIPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
| | | | | | | | | | | | | | | | | | | | | |
MSTNPKPKRKTKRNTNRRPQDVKFPGGGQIVGGVYLLRRRGPRLGVRATR
X           10           20           30           40           50

```

A3B465 *Genome polyprotein - Hepatitis C virus

20

```
ENTRY          A38465      #Type Protein
TITLE          *Genome polyprotein - Hepatitis C virus
DATE          30-Aug-1991 #Sequence 30-Aug-1991 #Text 21-Sep-1991
PLACEMENT      0.0        0.0        0.0        0.0        0.0
COMMENT        *This entry is not verified.
SOURCE         hepatitis C virus
REFERENCE
```

#Authors Takamizawa A., Mori C., Fuke I., Manabe S., Murakami
S., Fujita J., Onishi E., Andoh T., Yoshida I.,
30 Okayama H.

#Journal	J. Virol. (1991) 65:1105-1113
#Title	Structure and organization of the hepatitis C virus genome isolated from human carriers.

#Reference-number A38465

35 #Accession A38465

#Cross-reference EMBL: M58335

SUMMARY #Molecular-weight 327190 #Length 3010 #Checksum 7196
SEQUENCE

```

#Total Score      =      38   Optimized Score =      38   Significance = 30.99
Residue Identity  =     97%   Matches         =      38   Mismatches  =      1
Gaps              =      0    Conservative Substitutions =      0
Translation Frame =      1

```

45

```
X          10          20          30          X
STIPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRR
| | | | | | | | | | | | | | | | | | | | | |
MTSNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRAPR
X          10          20          30          40          50
```

50

A2B209 60K filarial antigen - Nematode (*Brugia malayi*)

```
ENTRY      A28209      #Type Protein
TITLE      60K filarial antigen - Nematode (Brugia malayi)
DATE       19-May-1989 #Sequence 19-May-1989 #Text 30-Sep-1991
PLACEMENT  0.0 0.0 0.0 0.0 0.0
SOURCE      Brugia malayi
ACCESSION  A28209
REFERENCE
```

```

#Authors      Nilsen T.W., Maroney P.A., Goodwin R.G., Perrine
              K.G., Denker J.A., Nanduri J., Kazura J.W.
10 #Journal    Proc. Natl. Acad. Sci. U.S.A. (1988) 85:3604-3607
#Title        Cloning and characterization of a potentially
              protective antigen in lymphatic filariasis.

```

#Reference-number A28209

#Accession A28209

```
15 #Molecule-type mRNA
    #Residues      1-548 (NIL)
```

#Cross-reference EMBL:J03266

SUMMARY	#Molecular-weight	62320	#Length	548	#Checksum	6506
---------	-------------------	-------	---------	-----	-----------	------

SEQUENCE

20

Initial Score = 13 Optimized Score = 16 Significance = 7.48

Residue Identity = 27% Matches = 19 Mismatches = 20

Gaps = 31 Conservative Substitutions = 0

Translation Frame= 1 1

၆၅

X 10 20 30
STIPKP-----QRKTKRNTNRRPQDVKFPGGGQIVGG-----

IAEAAERFMTDTINKPILLNRPSEIKAFYMQRDAKNTLTESVDLLMPGVGEIVGGSMRIWKFDELSKAFK
30420 430 440 450 460 470 480 490

$$\begin{array}{c} \text{X} \\ \text{--VYLLPRR} \\ | \quad | \\ 35 \text{ NVEIDPKPYWYLDQRLY} \\ \quad \quad 500 \end{array}$$

40

45

50

616363

FILE 'USPAT' ENTERED AT 10:32:25 ON 30 MAR 92

```
* * * * *
*           W E L C O M E   T O   T H E
*           U . S .   P A T E N T   T E X T   F I L E
* * * * *
```

=> file jpo

FILE 'JPOABS' ENTERED AT 10:32:49 ON 30 MAR 92

```
* * * * *
*           J A P A N E S E   P A T E N T   A B S T R A C T S
* * * * *
* CURRENTLY, DATA IS LOADED THROUGH THE ABSTRACT PUBLICATION
* DATE OF AUGUST 30, 1991.
* THE LATEST GROUPS RECEIVED ARE: C0862 E1105, M1150 & P1245.
* * * * *
```

=> s hepatitis

L1 293 HEPATITIS

=> s non (2w) hepatitis or (nanb?) or hcv

59371 NON

293 HEPATITIS

14 NON (2W) HEPATITIS

11 NANB?

3 HCV

L2 27 NON (2W) HEPATITIS OR (NANB?) OR HCV

=> s l2 and l1

L3 15 L2 AND L1

=> d 1-15 all

03-30676

Feb. 8, 1991

L3: 1 of 15

DNA OF NON-A, **NON**-B **HEPATITIS** VIRUS, THE CLONE AND ITS
PREPARATION

INVENTOR: MAKOTO HATTORI, et al. (4)

ASSIGNEE: SANWA KAGAKU KENKYUSHO CO LTD, et al. (40)

APPL NO: 01-163715

DATE FILED: Jun. 28, 1989

PATENT ABSTRACTS OF JAPAN

ABS GRP NO: C0825

ABS VOL NO: Vol. 15, No. 154

ABS PUB DATE: Apr. 18, 1991

INT-CL: C12N 15*51; //A61K 39*29

ABSTRACT:

NEW MATERIAL: A single stranded DNA containing about 850 nucleotides or a duplex DNA comprising the single stranded DNA and complimentary DNA, having a basic sequence to code part amino acid sequence of gene of

non-A, **non**-B **hepatitis** virus.

USE:Producing a raw material for diagnosticum and medicine for non-A, **non**-B **hepatitis**.

PREPARATION:For example, RNA is extracted from particle fraction of plasma derived from patient of non-A, **non**-B **hepatitis** and purified. EcoRI linker is added to duplex DNA fragment prepared by using the purified RNA as a template. Then the resulting substance is digested with restriction enzyme EcoRI, the prepared duplex DNA fragment is optionally separated into a single stranded DNA to give DNA having a basic sequence to code part of amino acid sequence of non-A, **non**-B **hepatitis** virus gene.1

02-186990 Jul. 23, 1990 L3: 2 of 15
cDNA CLONE OF POST-TRANSFUSION NON-A **NON**-B **HEPATITIS** VIRUS
(**NANB**) AND USE THEREOF

INVENTOR: MAKOTO HATTORI, et al. (4)
ASSIGNEE: SANWA KAGAKU KENKYUSHO CO LTD, et al. (90)
APPL NO: 01-4059
DATE FILED: Jan. 10, 1989
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C0767
ABS VOL NO: Vol. 14, No. 459
ABS PUB DATE: Oct. 4, 1990
INT-CL: C12N 15*51; A61K 39*29; C12N 7*02

ABSTRACT:

NEW MATERIAL:A cDNA clone such as phage clone YS1 or phage clone YS2 containing a nucleotide of about 5.4Kb coding the amino acid sequence of a post-transfusion non-A **non**-B **hepatitis** virus (**NANB**) and prepared by adding an EcoRI linker to a duplex cDNA fragment prepared by using a template consisting of a refined RNA existing in a particle fraction separated from serum and substituting and inserting the addition product to an EcoRI site of a lambda gt10 vector.

USE:Agent for the diagnosis, prevention and remedy of non-A **non**-B **hepatitis**. Blood cleaning agent for transfusion.

PREPARATION:The objective cDNA clone can be prepared e.g. by adding 20% polyethylene glycol to a plasma originated from a non-A **non**-B **hepatitis** patient, centrifuging the mixture at a high speed, solubilizing the precipitate with TEN buffer solution, etc., centrifuging at a high speed to collect purified RNA, preparing a duplex cDNA using the RNA as a template, adding an EcoRI linker to the cDNA and substituting and inserting the addition product to the EcoRI site of a lambda gt10 vector.e

01-124307 May 17, 1989 L3: 3 of 15
MANIFESTATION VECTOR HAVING DNA CODING NON-A **NON**-B **HEPATITIS**
SPECIFIC ANTIGEN, TRANSFORMANT AND PRODUCTION OF SAID ANTIGEN

INVENTOR: TATSURO SHIDUI, et al. (6)
ASSIGNEE: MITSUBISHI KASEI CORP
APPL NO: 62-263990
DATE FILED: Nov. 10, 1987
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C626
ABS VOL NO: Vol. 13, No. 367
ABS PUB DATE: Aug. 15, 1989
INT-CL: C12N 15*00; A61K 39*29; C12N 1*20; C12P 21*02; //(C12 P21*02;
C12R 1:19)

ABSTRACT:

PURPOSE: To produce a non-A **non**B **hepatitis** specific antigen, by introducing a DNA-containing DNA fragment coding a non-A **non**B **hepatitis** specific antigen in a cloning site existing at the downstream side of a promoter, thereby forming a manifestation vector.

CONSTITUTION: A DNA fragment containing a DNA coding a non-A **non**B **hepatitis** specific antigen is introduced into a cloning site existing at the downstream side of a promoter of manifestation vector. The obtained manifestation vector containing the DNA fragment is introduced into a host to effect the transformation of the host and the resultant transformant is cultured. The non-A **non**B **hepatitis** specific antigen produced and accumulated in the cultured product is separated therefrom. A large amount of non-A **non**B **hepatitis** specific antigen protein can be produced by this process at a low cost.

01-90197

Apr. 6, 1989
PEPTIDE

L3: 4 of 15

INVENTOR: SHIGETADA NAKANISHI, et al. (5)
ASSIGNEE: MITSUBISHI KASEI CORP
APPL NO: 62-246952
DATE FILED: Sep. 30, 1987
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C616
ABS VOL NO: Vol. 13, No. 302
ABS PUB DATE: Jul. 12, 1989
INT-CL: C07K 7*10; G01N 33*576; //A61K 39*29; C12N 15*00; C12P 21*00;
C07K 99:00

ABSTRACT:

NEW MATERIAL: A peptide, specifically reactive with a non-A, **non**B type **hepatitis** antigen mouse monoclonal antibody and having an amino acid sequence expressed by the formula or partial sequence thereof.

USE: A diagnostic reagent and vaccine for non-A, **non**B type **hepatitis** for screening transfusion blood or blood pharmaceuticals.

PREPARATION: For example, analysis of hydrophilicity and prediction of secondary structure of antigenic protein are carried out on the basis of an amino acid sequence found from the base sequence of a gene capable of coding a non-A, **non**B type **hepatitis** antigen to estimate a part which is a hydrophilic region for determining antigenicity on an antigenic protein from a part of a secondary structure, such as .alpha.-helix or turn. A peptide constituting the estimated part for determining the antigenicity is then synthesized by using an automatic synthetic apparatus for the peptide by a conventional method to afford the aimed peptide having the amino acid sequence expressed by the formula or partial sequence thereof.

64-2576

Jan. 6, 1989
DNA FRAGMENT

L3: 5 of 15

INVENTOR: KAZUNOBU TAKAHASHI, et al. (6)
ASSIGNEE: MITSUBISHI KASEI CORP
APPL NO: 62-140536
DATE FILED: Jun. 4, 1987
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C589
ABS VOL NO: Vol. 13, No. 171
ABS PUB DATE: Apr. 24, 1989
INT-CL: C12N 15*00; //(C12 N15*00; C12R 1:91)

ABSTRACT:

PURPOSE: To provide a DNA fragment containing a base sequence coding a non-A, **non**B **hepatitis** specific antigen protein and useful for the mass- production of a non-A, **non**B **hepatitis** specific antigen protein by a recombinant DNA technique.

CONSTITUTION: A liver tissue of a human or chimpanzee affected with non-A, **non**B **hepatitis** is homogenized in an aqueous solution of guanidium thiocyanate and whole RNA is separated as a precipitate by an equilibrium density gradient ultracentrifugation using cesium chloride. The separated whole RNA is purified by the extraction with phenol and the precipitation with ethanol. The RNA is further purified by oligo(dT)-cellulose column chromatography to separate a poly(A)-containing RNA, which is used as a raw material for mRNA. The objective DNA is determined from the mRNA through a cDNA library. The DNA is composed of a sequence of 1,333 bases.

61-176856

Aug. 8, 1986
NON-A **NON**B TYPE **HEPATITIS** ANTIGEN

L3: 6 of 15

INVENTOR: ISAO ONO, et al. (4)
ASSIGNEE: MITSUBISHI CHEM IND LTD, et al. (4)
APPL NO: 60-18201
DATE FILED: Feb. 1, 1985
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: P531
ABS VOL NO: Vol. 10, No. 389

ABS PUB DATE: Dec. 26, 1986
INT-CL: G01N 33*576; A61K 39*00; A61K 39*29; C12N 15*00; C12P 21*00;
G01N 33*577; //C07K 15*04

ABSTRACT:

PURPOSE: To make the diagnosis of a non-A **non**B **hepatitis** infection history, etc. possible by using an antigen which has about 1.17 approx. 1.26 density by a sucrose density-gradient centrifugation method and reacts with the antibody obtd. by transforming the lymphocyte of an individual body generated with the non-A **non**B type **hepatitis** by EB virus to obtain the positive culture cells for the non-A **non**B type **hepatitis** associated antibody then cloning the same.

CONSTITUTION: The liver tissue of the individual body generated with the non-A **non**B type **hepatitis** is homogenized and is then centrifugated for about 30 min. approx. 1 hr at about 8,000 approx. 1,000 rpm, then the tissue is subjected to ultracentrifugation at about 100,000g, by which the precipitate is obtd. The precipitate is further subjected to the sucrose density-gradient centrifugation by cane sugar, CsCl, KBr, etc. by which the precipitate is refined. The refining is executed by using the following antibody while assaying the antigen: The antibody obtd. by transforming the lymphocyte of the individual body generated with the non-A **non**B type **hepatitis** by the EB virus to obtain the positive culture cell for the non-A **non**B type **hepatitis** associated antibody, then cloning the same is used.

61-56196

Mar. 20, 1986
MONOCLONAL ANTIBODY

LS: 7 of 15

INVENTOR: ISAO ONO, et al. (2)
ASSIGNEE: ISAO ONO, et al. (4)
APPL NO: 59-147355
DATE FILED: Jul. 16, 1984
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C363
ABS VOL NO: Vol. 10, No. 219
ABS PUB DATE: Jul. 31, 1986
INT-CL: C07K 15*04; A61K 39*29; A61K 39*395; G01N 33*576; G01N 33*577;
//C12N 15*00; C12P 21*00

ABSTRACT:

PURPOSE: To provide the titled human and chimpanzee-type antibody reactive specifically with the antigen developed in hepatic cell in the crisis of a non-A non-B hepatitis of chimpanzee and man, and prepared by using the cloned cell of lymphocyte positive to the antibody relating to the chimpanzee and human non-A **non**B **hepatitis**.

CONSTITUTION: The peripheral blood lymphocyte of convalescent chimpanzee or man of non-A **non**B **hepatitis** is transformed by Epstein-Barr

virus to obtain culture cell positive to the antibody relating to non-A **non**B **hepatitis**, and the cell is cloned by a soft agar method, critical dilution method, etc. to obtain a cell strain (cloned strain) capable of producing the objective antibody. The obtained cloned strain is proliferated in e.g. a serum-free medium containing 0.5% bovine serum albumin, and the supernatant liquid is collected, subjected to ultrafiltration (to remove a fraction having a molecular weight of .ltoreq.300,000), and purified by gel-filtration chromatography (with 0.2M boric acid buffer solution of 9.0pH) to obtain the objective antibody.

61-25484

Feb. 4, 1985

L3: 8 of 15

CELL STRAIN PRODUCING ANTIBODY

INVENTOR: ISAO ONO, et al. (2)

ASSIGNEE: ISAO ONO, et al. (3)

APPL NO: 59-147354

DATE FILED: Jul. 16, 1984

PATENT ABSTRACTS OF JAPAN

ABS GRP NO: C355

ABS VOL NO: Vol. 10, No. 178

ABS PUB DATE: Jun. 21, 1986

INT-CL: C12N 5*00; //A61K 39*29; A61K 39*395; C07K 15*04; C12N 15*00;

C12P 21*00; G01N 33*576; G01N 33*577

ABSTRACT:

PURPOSE:To provide a cell strain originated from human and chimpanzee, capable of producing a monoclonal antibody reactive specifically to an antigen developing in the hepatic cell of non-A **non**B **hepatitis** and the screening of serum, etc.

CONSTITUTION:The peripheral blood lymphocyte of chimpanzee or human of the coalescence of non-A **non**B **hepatitis** is transformed with Epstein-Barr virus (EB virus), and the obtained culture cell positive to the antibody relating to non-A **non**B **hepatitis** is cloned to obtain the cell strain capable of producing the objective antibody. For example, the peripheral blood of a chimpanzee or human of the coalescence of non-A **non**B **hepatitis** is collected and added with heparin, and lymphocyte is separated from the blood by centrifugal separation. Separately, the cell producing and releasing EB virus is cultured in a medium, and the supernatant liquid of the culture product is separated to obtain a virus source. The virus source is made to contact with the above lymphocyte, inoculated in a micro-titer plate for tissue culture at various cultivation densities, and cultured to obtain the objective strain.

60-176600

Sep. 10, 1985

L3: 9 of 15

METHOD FOR MEASURING ACTIVITY OF GUANASE

INVENTOR: NOBUYUKI IWAMOTO, et al. (2)

ASSIGNEE: KK FUJIMOTO RINSHIYOU KENSA KENKYUSHO

APPL NO: 59-34760

DATE FILED: Feb. 24, 1984
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C325
ABS VOL NO: Vol. 10, No. 23
ABS PUB DATE: Jan. 29, 1986
INT-CL: C12Q 1*48; G01N 33*50

ABSTRACT:

PURPOSE: To determine accurately, rapidly and easily the activity of guanase useful for non A or **non** B **hepatitis**, by using a measuring reagent containing guanaine, xanthine oxidase, etc.

CONSTITUTION: A buffer solution of 6. approx. 9pH containing guanine or oxidized form tetrazolium or a halide thereof and xanthine oxidase is used as a measuring reagent, and a humoral sample is added thereto to convert guanine into xanthine by guanase in the sample. The resultant xanthine is converted into uric acid by xanthine oxidase, and the oxidized form tetrazolium is reduced to give reduced form tetrazolium (formazan) by superoxide anion. The absorbance of a characteristic absorption band of the formed formazan is measured.

02-89430

May 20, 1985

L3: 10 of 15

NON-A, multidot. **NON** B-TYPE **HEPATITIS** RELATING ANTIGEN

INVENTOR: HITOSHI OOHORI, et al. (1)
ASSIGNEE: SENDAI BISEIBUTSU KENKYUSHO
APPL NO: 58-197356
DATE FILED: Oct. 20, 1983
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C303
ABS VOL NO: Vol. 9, No. 220
ABS PUB DATE: Sep. 13, 1985
INT-CL: A61K 39*00; //A61K 35*22; G01N 33*570

ABSTRACT:

PURPOSE: To provide the titled antigen composed of the protein recovered from the urine, blood, etc. of a non-A, multidot. **non** B-type **hepatitis** patient, and useful for the remedy and diagnosis of non-A, multidot. **non** B-type **hepatitis**.

CONSTITUTION: The urine, blood (preferably blood plasma), etc. of a non-A, multidot. **non** B-type **hepatitis** patient is used as a raw material, is subjected to a proper combination of the concentration, the fractionation taking advantage of the solubility difference, the ion exchange material treatment, the gel filtration, etc. to obtain the objective SO antigen having the following characteristics: (i) electrophoretic analysis, moves toward the .beta.-region; (ii) molecular weight, about 250,000, decomposed to a fraction having a molecular weight of about 38,000 by electrophoresis; (iii) electron microscopic observation, granular structure having a diameter of 11nm; (iv)

exhibiting the antigenicity to animal; and (v) causing strong agglutination reaction with the serum and urine of only the non-A, multidot. **non**B-type **hepatitis** patient by the RPHA reagent prepared from the refined antigen. A reagent to detect the relating antibody can be produced by bonding said antigen with a carrier, and a vaccine is prepared by treating the antigen at 60 degrees C. for 10hr or treating with formalin.

58-183629 Oct. 26, 1983 L3: 11 of 15
MONOCLONAL ANTIBODY AND DIAGNOSTIC AGENT RELATING TO NON-A AND **NON**B
TYPE **HEPATITIS**

INVENTOR: TOSHITAKA AKATSUKA, et al. (2)
ASSIGNEE: EISAI KK
APPL NO: 57-65430
DATE FILED: Apr. 21, 1982
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C206
ABS VOL NO: Vol. 8, No. 15
ABS PUB DATE: Jan. 21, 1984
INT-CL: A61K 39*395; A61K 39*44; G01N 33*54

ABSTRACT:

PURPOSE: The titled monoclonal antibody that is obtained by isolating from autopsic livers with non-A and **non**B type **hepatitis** and purifying the product, thus being used as an ingredient of a diagnostic agent for non-A and non-B hepatitis, because of its showing characteristic antigen-antibody reaction with antigens relating to non-A and **non**B type **hepatitis**.

CONSTITUTION: The objective monoclonal antibody is obtained by isolating from autopsic livers with non-A and **non**B type **hepatitis** and purifying the product, shows a characteristic reaction with antigens relating to the above **hepatitis** and has following physical and chemical properties: molecular weight, more than 1,500,000 (by the gel filtration method); sedimentation constant (10^{sup}, -^{sup}1^{sup}), 51.5S (by the ultracentrifugation method); floating density (g/cm^{sup}3), 1.15 approx. 1.25 (in CsCl or KBr); particle size (nm), 26 approx. 37; electric mobility, in the α_2 - α_1 globulin region (in the agarose gel). It is used as a diagnostic agent containing the antibody as a major ingredient, e.g., in the reverse passive hemagglutination method using sheep sensitized erythrocytes or the antibody sandwich method using sensitized glass beads.

58-753 Jan. 5, 1983 L3: 12 of 15
NON-A AND **NON**B TYPE **HEPATITIS** RELATED ANTIBODY AND DETECTION
REAGENT

INVENTOR: JIYUNICHI FUJIMATSU, et al. (2)
ASSIGNEE: EISAI KK
APPL NO: 56-97425
DATE FILED: Jun. 25, 1981

PATENT ABSTRACTS OF JAPAN

ABS GRP NO: P185

ABS VOL NO: Vol. 7, No. 70

ABS PUB DATE: Mar. 23, 1983

INT-CL: G01N 33*54; A61K 39*395

ABSTRACT:

PURPOSE: To obtain a superior detection reagent of non-A and **non**B type **hepatitis**, by combining antigen having a specific property which is separated and refined from non-A and **non**B type **hepatitis** part liver and a singular antibody obtained by injecting to an animal with a minute particle, enzyme etc.

CONSTITUTION: Non-A and **non**B **hepatitis** antigen having .gtorog.150 ten thousand molecular weight by measured value of a gel filtration method, 51.5.times.10.sup.-sup.1.sup.38 precipitation constant by an ultra centrifugal analysing method, 1.15.approx.1.25g/cm.sup.3 floating density in CsCl and KBr, 26.approx.37nm grain diameter and .alpha..sub.2-.alpha..sub.1 electric transfer degree in globulin domain (in agarose gel), is obtained by separating from non-A and **non**B **hepatitis** part liver and refining it. Immunity is given to a house rabbit by this antigen and an antibody is obtained by carrying out IgG refining graduation of an antiserum. The highly accurate detection is made possible by using a combined body combined this antibody with fine particle of a red blood corpuscle of sheep etc., an isotope of .sup.1.sup.2.sup.51 etc, or an enzyme of alkali phosphatase etc. for the detection of non-A and non-B hepatitis antigen or using for a reagent for diagnosis of a patient or inspection of blood for blood transfusion.

57-198867

Dec. 6, 1982

L3: 13 of 15

NON-A, **NON**B **HEPATITIS** RELATED ANTIGEN AND DIAGNOSTIC THEREFOR

INVENTOR: JIYUNICHI FUJIMATSU, et al. (2)

ASSIGNEE: EISAI KK

APPL NO: 56-83736

DATE FILED: Jun. 2, 1981

PATENT ABSTRACTS OF JAPAN

ABS GRP NO: P179

ABS VOL NO: Vol. 7, No. 51

ABS PUB DATE: Feb. 26, 1983

INT-CL: G01N 33*54; A61K 39*29

ABSTRACT:

PURPOSE: To enable a reliable diagnosis and curing of non-A, **non**B **hepatitis**, by using a non-A, **non**B **hepatitis** related antigen separated and refined from an autopsy liver of a non-A, **non**B **hepatitis** patient, or a conjugate of said antigen with a sheep erythrocyte, an isotope, an enzyme or the like as a diagnostic.

CONSTITUTION: A non-A, **non**B **hepatitis** related antigen, which has

MW of 1,500,000 or more (by a gel filtration method), a sedimentation constant (10.sup.-sup.1.sup.2) of 51.SS (by an ultracentrifugal analysis), a buoyant density (g/cm.sup.2) of 1.15.approx. 1.25 (in cesium chloride and in KBr), a particle diameter (nm) of 26.approx.37, and an electrophoretic mobility in an .alpha..sub.2-.alpha..sub.1 globulin region in agarose gel, is separated and refined from an autopsy liver of a non-A, **non**-B **hepatitis** patient by a specified treatment. A conjugate of the obtained antigen with a minute particle such as sheep erythrocyte, an isotope such as .sup.1.sup.2.sup.51, alkali phosphatase or the like is prepared to obtain a diagnostic for immunological analysis. Thus a diagnostic which clearly distinguishes non-A, **non**-B **hepatitis** from other **hepatitis**.

57-175127 Oct. 28, 1982 L3: 14 of 15
SUBSTANCE AND VACCINE RELATED TO **HEPATITIS** **NANB**-1 ANDNANB-2 VIRAL
ANTIGEN

INVENTOR: KOUJI YOSHIKAWA, et al. (1)
ASSIGNEE: TETSUO NAKAMURA
APPL NO: 56-60221
DATE FILED: Apr. 21, 1981
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: C147
ABS VOL NO: Vol. 7, No. 19
ABS PUB DATE: Jan. 25, 1983
INT-CL: A61K 39*29

ABSTRACT:

PURPOSE:To obtain the titled vaccine, having a high immunogenicity without infection, and useful for a detecting reagent of the titled viral antigen, by treating **hepatitis** **NANB**-1 and **NANB**-2 viral particles with an organic solvent, and heat-treating the particles.

CONSTITUTION:Viral particles, obtained from the blood serum of the **hepatitis** **NANB**-1 in the acute stadium, and found to be capable of agglutinating with the **hepatitis** **NANB**-1 blood serum in the decubation and infecting and developing the typical **hepatitis** **NANB**-1 in sensitive animals are inactivated by the addition of an organic solvent, e.g. 37% formalin, and the heat-treatment (50.degrees C. for 10hr) to give a **hepatitis** **NANB**-1 viral vaccine. Similarly, the **hepatitis** **NANB**-2 viral vaccine is obtained. The resultant respective specific antibodies of the hepatic viruses permit the detection of the new **hepatitis** **NANB**-1 and **NANB**-2 viral antigens capable of infecting and developing the **hepatitis** non-A and non-B.

55-122156 Sep. 19, 1980 L3: 15 of 15
C-TYPE **HEPATITIS** VIRUS-ASSOCIATED ANTIGEN

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ASSIGNEE: KAGAKU OYOBI KETSUSEIRIYOHOU KENKYUSHO
APPL NO: 54-30332

DATE FILED: Mar. 14, 1979
PATENT ABSTRACTS OF JAPAN
ABS GRP NO: P040
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ABS PUB DATE: Dec. 12, 1980
INT-CL: G01N 33*54; A61K 39*29

ABSTRACT:

PURPOSE: To obtain C-type **hepatitis** virus-associated antigen by separating a special antigen from blood plasma (serum) of a patient diagnosed as non-A-type or **non** B-type **hepatitis** after he had been subjected to transfusion of HBs antigen-negative blood.

CONSTITUTION: Blood plasma (serum) of a patient diagnosed as non-A-type or **non** B-type **hepatitis** with multi-peak rise in GPT in particular and with a comparatively long period of incubation, obtained in the acute stage is used as a starting substance. This substance is subjected to gel filtration to obtain fractions (based on absorbance measurement of about 280nm). Among these fractions, one corresponding to a third peak P.sub.3 (refer to the drawing) is collected and subjected to column chromatography using an ion exchanger. The resulting product is condensed as necessary by using a precipitation method with polyethylene glycol, and refined by an ultra-centrifugal separation to obtain an objective antigen.

=> file uspat
FILE 'USPAT' ENTERED AT 10:36:30 ON 30 MAR 92

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*           WELCOME TO THE           *
*           U. S.  PATENT  TEXT  FILE  *
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=> s 436820/cclv
L4 119 436820/CCLR

=> d 1-10

1. 5,091,300, Feb. 25, 1992, Radio-immuno assay for hepatitis B virus
PreS2 antibodies; William M. Hurri, et al., 435/5, 235.1, 810, 940;
436/501, 518, 534, 543, 547, 804, 808, **820** [IMAGE AVAILABLE]
2. 5,073,481, Dec. 17, 1991, Assay to detect the presence of live virus
in vitro; Jerome B. Zeldis, et al., 435/5; 424/89; 435/29, 233;
436/820 [IMAGE AVAILABLE]
3. 5,061,619, Oct. 29, 1991, Immunoassay using antibody-antigen
conjugates; Strathearn Wilson, et al., 435/5, 7.1, 7.9, 7.92, 7.94;
436/507, 509, 512, 513, 518, 536, 540, **820** [IMAGE AVAILABLE]
4. 5,038,555, Jul. 9, 1991, Membrane-strip reagent serodiagnostic
apparatus and method; Roger M. Clemmons, 435/5; 422/56, 57, 58; 435/7.94,

288, 299, 300, 301, 311, 305, 310; 436/177, 178, 510, 528, 530, 531, 535, 808, 810, 811, 813, **820** [IMAGE AVAILABLE]

5. 4,952,494, Aug. 28, 1990, Assay to detect the presence of live non-A, non-B hepatitis agents in vitro; Jerome B. Zeldis, et al., 435/5, 29, 32, 236; **436/820** [IMAGE AVAILABLE]

6. 4,912,030, Mar. 27, 1990, Viral isolates and their use in diagnosis; Robin Weiss, et al., 435/5; 424/89, 93T; 435/93, 188, 810, 974, 975; 436/518, 531, 543, 547, 804, 808, 809, 810, 815, **820**, 823

7. 4,879,219, Nov. 7, 1989, Immunoassay utilizing monoclonal high affinity IgM antibodies; Jack R. Wands, et al., 435/5; 424/1.1, 85.8, 89; 435/240.27, 948; 436/503, 504, 536, 537, 538, 539, 540, 541, 542, 804, 811, **820**; 530/387, 389, 826 [IMAGE AVAILABLE]

8. 4,871,659, Oct. 3, 1989, Reagent for detecting non-A, non-B viral hepatitis (NANBH) and an immunoenzymatic method for detecting NANBH antigens in fecal extracts; Jacques Pillot, 435/5; 422/61; 435/7.94, 810; 436/513, 531, 808, **820**

9. 4,853,326, Aug. 1, 1989, Carbohydrate perturbations of viruses or viral antigens and utilization for diagnostic prophylactic and/or therapeutic applications; Gerard A. Quash, et al., 435/5, 974; 436/507, 518, 543, 548, 812, **820**

10. 4,839,298, Jun. 13, 1989, Virus inactivating diluents used in immunoassays; John W. D. Kay, et al., 436/175; 424/89, 531; 435/5, 238, 974; 436/22, 174, 176, 536, **820**

=> d 11-20

11. 4,839,277, Jun. 13, 1989, Method for purification of HBe antigen and method for measurement of HBe antibody by using said purified HBe antigen; Keishin Sugahara, et al., 435/5, 69.3, 239; **436/820**; 935/68, 69

12. 4,837,167, Jun. 6, 1989, Immunoassay for multi-determinant antigens using high-affinity; Hubert J. P. Schoemaker, et al., 435/5; 424/86; 435/7.94; 436/513, 518, 536, 540, 542, 548, 804, 819, **820**; 530/387, 806; 935/107, 109, 110

13. 4,818,608, Apr. 4, 1989, Assays for antibody to hepatitis B core antigen; Marina Adamich, et al., 435/5; 424/85.8, 86; 435/7.93, 70.21, 172.2, 240.27, 810, 948; 436/518, **820**

14. 4,803,156, Feb. 7, 1989, Peptide-beta-lactamase conjugates for enzyme-linked immunoassays; Alexander R. Neurath, et al., 435/5, 7.92, 18, 19; **436/820**, 828; 930/142, 200, 221, 222, 223, 260, 310, DIG.820

15. 4,783,138, Nov. 29, 1988, Method to achieve a linear standard curve in a sandwich immunoassay; Ker-Kong Tung, et al., 435/5, 7.23, 7.4, 7.5, 7.7, 7.94; 436/513, 533, 534, 801, 803, 817, **820**, 827

16. 4,752,562, Jun. 21, 1988, Detection of serum antibody and surface antigen by radial partition immunoassay; Mark I. Shelman, et al., 435/5, 7.22, 7.31, 29; 436/514, 515, 519, 527, 535, 541, **820**

17. RE 32,636, Jun. 14, 1988, Enzymatic immunological method for determination of antigens and antibodies; Antonius H. W. M. Schuurs, et al., 425/5, 7.93, 810; 436/519, 531, 532, 808, **820**

18. 4,727,019, Feb. 23, 1988, Method and apparatus for immunoassays; Gunars E. Valkirs, et al., 435/5, 6, 7.34, 7.4, 7.5, 287, 974; 436/513, 519, 527, 531, 548, 807, 818, **820**, 824

19. 4,707,542, Nov. 17, 1987, Immunogenic HbsAg derived from transformed yeast; Arthur Friedman, et al., 530/371; 210/198.2, 502.1, 635; 424/89; 435/5, 69.3, 71.1, 172.3, 235.1, 239, 255, 803; **436/820**; 530/395, 415, 417, 806, 826

20. 4,707,439, Nov. 17, 1987, Screening test for reverse-transcriptase containing virus such as non-A, non-B hepatitis, NANBH; Belinda P. Seto, et al., 435/5; 424/3; 435/4, 6; **436/820**; 935/76 [IMAGE AVAILABLE]

=> d his

(FILE 'USPAT' ENTERED AT 10:32:25 ON 30 MAR 92)

FILE 'JP0088' ENTERED AT 10:32:49 ON 30 MAR 92

L1 293 S HEPATITIS
L2 27 S NON (2W) HEPATITIS OR (NANB?) OR HCV
L3 15 S L2 AND L1

FILE 'USPAT' ENTERED AT 10:36:30 ON 30 MAR 92

L4 119 S 436820/CCLR

=> s 12

536033 NON
2749 HEPATITIS
108 NON (2W) HEPATITIS
200 NANB?
40 HCV
L5 321 NON (2W) HEPATITIS OR (NANB?) OR HCV

=> s 11

L6 2749 HEPATITIS

=> s 11 and 15

L7 113 L1 AND L5

=> d 1-20

1. 5,099,002, Mar. 24, 1992, Sequential improved method for treatment of human blood-clotting factor products; Alan I. Rubinstein, 530/381; 424/530; 514/8, 12, 21; 530/380, 382, 383, 384 [IMAGE AVAILABLE]

2. 5,097,013, Mar. 17, 1992, Sequential heat treatment of blood-clotting factor products; Alan I. Rubinstein, 530/303; 424/530; 514/0, 12, 21; 530/381 [IMAGE AVAILABLE]

3. 5,094,950, Mar. 10, 1992, Removal of process chemicals from labile biological mixtures by hydrophobic interaction chromatography; Richard J. Bonow, 436/170; 210/656; 435/69.5 [IMAGE AVAILABLE]

4. 5,087,572, Feb. 11, 1992, DNA encoding human plasminogen modified at the cleavage site; Francis J. Castellino, et al., 435/240.2, 217, 252.3, 255, 320.1; 536/27 [IMAGE AVAILABLE]

5. 5,077,193, Dec. 31, 1991, Non-A, **Non**B **hepatitis** virus genome RNA, cDNA and virus antigen protein; Shunji Mishiro, et al., 435/5, 6; 436/94, 501; 536/26, 27, 28 [IMAGE AVAILABLE]

6. 5,077,192, Dec. 31, 1991, Method of detecting antigenic, nucleic acid-containing macromolecular entities; Tsanyang Liang, et al., 435/5, 6, 7.1, 7.2 [IMAGE AVAILABLE]

7. 5,075,425, Dec. 24, 1991, Process for the preparation of a pharmaceutical which contains IgG, IgA and IgM and can be administered intravenously; Ronald Kotitschke, et al., 530/387; 424/85.8 [IMAGE AVAILABLE]

8. 5,063,054, Nov. 5, 1991, Microbial products used for treatment of **hepatitis**; Joseph Chang, 424/92, 195.1, 520; 435/824 [IMAGE AVAILABLE]

9. 5,061,227, Oct. 29, 1991, Method of purifying whole blood; Reiner Gessler, et al., 604/5; 436/512 [IMAGE AVAILABLE]

10. 5,055,485, Oct. 8, 1991, Inactivation of viruses in cell- and protein-containing compositions using aryl diol epoxides; Nicholas E. Geacintov, et al., 514/449; 424/529, 530, 531, 583; 435/1, 2; 514/2 [IMAGE AVAILABLE]

11. 5,041,078, Aug. 20, 1991, Photodynamic viral deactivation with sapphyrins; J. Lester Matthews, et al., 604/4; 540/145 [IMAGE AVAILABLE]

12. 5,036,072, Jul. 30, 1991, Antiviral agent; Tsunetaka Nakajima, et al., 514/274, 346, 351 [IMAGE AVAILABLE]

13. 5,032,511, Jul. 16, 1991, DNA fragments coding for antigens specific to non-A **non**B **hepatitis**, expression vectors containing said DNA fragments, transformants and process for producing said antigens; Kazuhiro Takahashi, et al., 435/69.1, 91, 172.3, 225.1, 240.1, 252.31, 252.33, 320.1; 530/350; 536/27; 935/18, 27, 31, 41, 56, 57, 65, 70, 73, 74, 81 [IMAGE AVAILABLE]

14. 5,013,305, May 7, 1991, Needle safety system and method; Eric A. Opitz, et al., 604/192, 198, 263 [IMAGE AVAILABLE]

15. 5,005,793, Apr. 9, 1991, Pole clip needle cap holder; Richard A.

Shillington, 248/229, 230, 912 [IMAGE AVAILABLE]

16. 5,004,688, Apr. 2, 1991, Purification of **hepatitis** proteins; William S. Craig, et al., 435/69.3, 235.1; 530/350 [IMAGE AVAILABLE]

17. 4,994,438, Feb. 19, 1991, Heat treatment of lyophilized plasma fractions; Alan Rubinstein, 514/2; 424/530 [IMAGE AVAILABLE]

18. 4,994,046, Feb. 19, 1991, Needle guard for syringe; Vann T. Wesson, et al., 604/198; 128/919; 604/263 [IMAGE AVAILABLE]

19. 4,979,616, Dec. 25, 1990, Syringe disposal container; Dennis L. Clanton, 206/364, 523; 220/4.24 [IMAGE AVAILABLE]

20. 4,971,760, Nov. 20, 1990, Novel method for disinfecting red blood cells, blood platelets, blood plasma, and optical corneas and sclerae; Alan I. Rubinstein, 422/37, 28; 435/2; 514/833; 530/385 [IMAGE AVAILABLE]

=> s hepatitis/ti,ab
153 HEPATITIS/TI
235 HEPATITIS/AB
L8 253 HEPATITIS/TI,AB

=> s 18 and 17
L9 33 L8 AND L7

=> d 1-33

1. 5,099,002, Mar. 24, 1992, Sequential improved method for treatment of human blood-clotting factor products; Alan I. Rubinstein, 530/381; 424/530; 514/8, 12, 21; 530/380, 382, 383, 384 [IMAGE AVAILABLE]

2. 5,097,010, Mar. 17, 1992, Sequential heat treatment of blood-clotting factor products; Alan I. Rubinstein, 530/383; 424/530; 514/0, 12, 21; 530/381 [IMAGE AVAILABLE]

3. 5,077,193, Dec. 31, 1991, Non-A, **Non**B **hepatitis** virus genome RNA, cDNA and virus antigen protein; Shunji Mitsuoka, et al., 435/5, 6; 436/94, 501; 536/26, 27, 28 [IMAGE AVAILABLE]

4. 5,063,054, Nov. 5, 1991, Microbial products used for treatment of **hepatitis**;; Joseph Chang, 424/92, 195.1, 520; 435/824 [IMAGE AVAILABLE]

5. 5,032,511, Jul. 16, 1991, DNA fragments coding for antigens specific to non-A **non**B **hepatitis**, expression vectors containing said DNA fragments, transformants and process for producing said antigens; Kazuhiro Takahashi, et al., 435/69.1, 91, 172.3, 235.1, 240.1, 252.31, 252.33, 320.1; 530/350; 536/27; 935/19, 27, 31, 41, 56, 57, 65, 70, 73, 74, 81 [IMAGE AVAILABLE]

6. 5,004,688, Apr. 2, 1991, Purification of **hepatitis** proteins; William S. Craig, et al., 435/69.3, 235.1; 530/350 [IMAGE AVAILABLE]

7. 4,952,494, Aug. 28, 1990, Assay to detect the presence of live non-A, **non-B hepatitis** agents in vitro; Jerome B. Zeldis, et al., 435/5, 29, 32, 226; 436/820 [IMAGE AVAILABLE]

8. 4,871,659, Oct. 3, 1989, Reagent for detecting non-A, **non-B** viral **hepatitis** (**NANBH**) and an immunoenzymatic method for detecting **NANBH** antigens in fecal extracts; Jacques Pillot, 435/5, 422/61; 435/7.94, 810; 436/513, 531, 808, 820

9. 4,870,829, Sep. 26, 1989, Non-A, **non-B hepatitis** virus, methods of identification purification, characterization, diagnosis and immunization; Jack Wands, et al., 436/548; 424/85.8, 89

10. 4,820,805, Apr. 11, 1989, Undenatured virus-free trialkyl phosphate treated biologically active protein derivatives; Alexander R. Neurath, et al., 530/410; 424/89; 530/391, 406, 808, 829

11. 4,777,245, Oct. 11, 1988, Non-human primate monoclonal antibodies and methods; Steven K. H. Fong, et al., 530/387; 424/1.1, 85; 435/5, 7.23, 70.21, 172.2, 172.3, 188, 240.27, 948; 935/96 [IMAGE AVAILABLE]

12. 4,764,369, Aug. 16, 1988, Undenatured virus-free biologically active protein derivatives; Alexander R. Neurath, et al., 424/89, 85.8; 435/236; 514/8

13. 4,787,439, Nov. 17, 1987, Screening test for reverse-transcriptase containing virus such as non-A, **non-B hepatitis**, **NANBH**; Belinda P. Seto, et al., 435/3; 424/3; 435/4, 6; 436/820; 935/76 [IMAGE AVAILABLE]

14. 4,702,909, Oct. 27, 1987, Non-A, **non-B hepatitis** antigen, antigen compositions, vaccine and diagnostic reagent; Victor M. Villarejos, et al., 424/89; 435/5, 235.1, 239; 436/5, 543, 820

15. 4,673,634, Jun. 16, 1987, Purified antigen from non-A, **non-B hepatitis** causing factor; Belinda Seto, et al., 435/5; 424/86, 89; 435/7.9, 810, 961; 436/543, 547, 820; 530/387, 395, 826

16. 4,615,886, Oct. 7, 1986, Utilizing a halohydrocarbon containing dissolved water to inactivate a lipid virus; Robert H. Purcell, et al., 514/2; 424/529, 530; 514/8

17. 4,591,585, May 27, 1986, Process for inactivating **hepatitis B** virus; Alfred M. Prince, 424/530; 435/236

18. 4,581,231, Apr. 8, 1986, Inactivation of viruses containing essential lipids; Robert H. Purcell, et al., 424/530; 435/238; 514/2; 530/383

19. 4,548,016, Sep. 17, 1985, Non-a **non-b hepatitis** surface antigen useful for the preparation of vaccines and methods of use; Christian Trepo, 424/86, 89

20. 4,548,573, Sep. 10, 1985, Undenatured virus-free biologically active

protein derivatives; Alexander R. Neurath, et al., 530/381; 424/529, 531, 534; 514/2, 5; 530/351, 359, 364, 380, 382, 383, 384, 385, 386, 387, 392, 393, 394, 829, 830, 831

21. 4,511,550, Apr. 16, 1985, Inactivation of a lipid virus; Robert H. Purcell, et al., 514/743; 424/89; 435/230; 514/758

22. 4,495,278, Jan. 22, 1985, Process for making novel blood clotting enzyme compositions; William R. Thomas, 435/5

23. 4,491,632, Jan. 1, 1985, Process for producing antibodies to **hepatitis** virus and cell lines therefor; Jack R. Wands, et al., 435/240.27; 424/86; 435/172.2; 935/103

24. 4,481,189, Nov. 6, 1984, Process for preparing sterilized plasma and plasma derivatives; Alfred M. Prince, 424/530; 514/2; 530/303

25. 4,464,474, Aug. 7, 1984, Non-A, **non**B **hepatitis** assay and vaccine; Pierre L. J. Coursaget, et al., 436/513, 531, 804, 820

26. 4,456,590, Jun. 26, 1984, Heat treatment of lyophilized blood clotting factor VIII concentrate; Alan Rubinstein, 530/383; 514/2

27. 4,438,098, Mar. 20, 1984, Heat treatment of a non-A, **non**B **hepatitis** agent to prepare a vaccine; Edward Tabor, et al., 424/89; 435/235.1, 236, 239

28. 4,385,395, Jul. 26, 1983, Detection of non-A, **non**B **hepatitis** associated antigen; Edward Tabor, et al., 424/89; 436/516; 530/806

29. 4,356,164, Oct. 26, 1982, Detection of non-A, **non**B **hepatitis** associated antigen; Edward Tabor, et al., 435/5, 7.25, 906; 436/515, 516, 520, 522, 532, 542, 820 IMAGE AVAILABLE

30. 4,314,997, Feb. 9, 1982, Purification of plasma protein products; Edward Shanbrun, 514/2, 8, 21

31. 4,291,020, Sep. 22, 1981, Inactivation of non-A, **non**B **hepatitis** agent; Edward Tabor, et al., 424/89; 435/230

32. 4,271,145, Jun. 2, 1981, Process for producing antibodies to **hepatitis** virus and cell lines therefor; Jack R. Wands, et al., 530/387; 424/86, 88, 89; 435/172.2, 240.27, 949; 935/70, 107, 108, 110

33. 4,021,540, May 3, 1977, Preparation of a **hepatitis** B immune globulin and use thereof as a prophylactic material; William Pollack, et al., 424/86; 436/544, 545, 804, 820; 530/387, 830, 831

=> J hlg

(FILE 'USPAT' ENTERED AT 10:32:25 ON 30 MAR 92)

FILE 'JPOASB' ENTERED AT 10:32:49 ON 30 MAR 92

L1 293 S HEPATITIS
L2 27 S NON (2W) HEPATITIS OR (NAND?) OR HCV
L3 15 S L2 AND L1

FILE 'USPAT' ENTERED AT 10:36:30 ON 30 MAR 92

L4 119 S 436020/CCLR
L5 321 S L2
L6 2746 S L1
L7 113 S L1 AND L5
L8 253 S HEPATITIS/TI,AB
L9 32 S L3 AND L7

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U.S. Patent & Trademark Office LOGOFF AT 10:41:29 ON 30 MAR 92

Get Items Description

?s non? (w) hepatitis or (Nan?HCH?Hnanb?) or (hcv)

5))File 5 processing for NON? stopped at NONAUTOXIDIZABILITY
)))File 155 processing for NON? stopped at NONCENTROCYTIC
 Processing
)))File 399 processing for NON? stopped at NONANETRIONES
)))File 351 processing for NON? stopped at NONLEADED
 10))File 350 processing for NON? stopped at NONSHATTERING
 Processing
 1817201 NON?
 105824 HEPATITIS
 46 NON?(W)HEPATITIS
 15 1018 NANB?
 1588 HCV
 S1 2473 NON? (W) HEPATITIS OR (NANB?) OR (HCV)
 ?s antigen?
 Processing
 20 S2 568407 ANTIGEN?
 ?s s1 and s2
 Processing
 2473 S1
 568407 S2
 25 S3 624 S1 AND S2
 ?s core
 S4 201124 CORE
 ?s s3 and s4
 30 624 S3
 201124 S4
 S5 129 S3 AND S4
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 35
)))Duplicate detection is not supported for File 351.
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 40))Record 5:7760384 ignored; incomplete bibliographic data.
 ...examined 50 records (50)
 ...examined 50 records (100)
 ...completed examining records
 S6 99 RD 95 (unique items)
 45t s6/3/1-99

6/3/1 (Item 1 from file: 5)
 9003761 BIOSIS Number: 92078761
 50 HEPATITIS C VIRUS INFECTION AS A RISK FACTOR FOR HEPATOCELLULAR CARCINOMA
 IN PATIENTS WITH CIRRHOSIS A CASE-CONTROL STUDY
 SIMONETTI R G; CAMMA C; FIORELLO F; COTTONE M; RAPICETTA M; MARINO L;
 FIORENTINO G; CRAXI A; CICCAGLIONE A; ET AL
 DIV. MED., OSPEDALE CERVELLO, VIA TRABUCCO 180, 90146 PALERMO, ITALY.

ANN INTERN MED 116 (2). 1992. 97-102. CODEN: AIMEA
Full Journal Title: Annals of Internal Medicine
Language: ENGLISH

56/3/2 (Item 2 from file: 5)
9092070 BIOSIS Number: 93077070
HEPATITIS C VIRUS ANTIBODY SECRETION IN-VITRO BY PERIPHERAL BLOOD
LYMPHOCYTES
LOEHR H; FLEISCHER B; MICHEL G; ROSSOL S; HESS G; MEYER ZUM BUESCHENFELDE
10-H; MANNS M
J. DEP. MED., UNIV. MAINZ, LANGENBECKSTRASSE 1, 6500 MAINZ, FRG.
J HEPATOL (AMST) 14 (1). 1992. 112-117. CODEN: JOHEE
Full Journal Title: Journal of Hepatology (Amsterdam)
Language: ENGLISH

15
6/3/3 (Item 3 from file: 5)
9081796 BIOSIS Number: 93066796
THE PREVALENCE OF ANTI-HEPATITIS C VIRUS AMONG CHINESE PATIENTS WITH
HEPATOCELLULAR CARCINOMA
20 LEE S-D; LEE F-Y; WU J-C; HWANG S-J; WANG S-S; LO K-J
DIV. GASTROENTEROL., VETERANS GEN. HOSP., TAIPEI, TAIWAN 11217, CHINA.
CANCER (PHILA) 69 (2). 1992. 342-345. CODEN: CANCA
Full Journal Title: CANCER (Philadelphia)
Language: ENGLISH

25
6/3/4 (Item 4 from file: 5)
9081193 BIOSIS Number: 93066193
IGM-ANTIBODY RESPONSE TO HEPATITIS C VIRUS ANTIGENS IN ACUTE AND CHRONIC
POST-TRANSFUSION NON-A NON-B HEPATITIS
30 CHAU K H; DAWSON G J; MUSHAWWAR I K; GUTIERREZ R A; JOHNSON R G;
LESNIEWSKI R R; MATSSON L; WEILAND O
EXPERIMENTAL BIOL. RESEARCH, ABBOTT LAB., NORTH CHICAGO, ILL., USA.
J VIROL METHODS 35 (3). 1991. 343-352. CODEN: JUMED
Full Journal Title: Journal of Virological Methods
35 Language: ENGLISH

6/3/5 (Item 5 from file: 5)
9069233 BIOSIS Number: 93054233
ANTIBODIES TO RECOMBINANT AND SYNTHETIC PEPTIDES DERIVED FROM THE
40 HEPATITIS C VIRUS GENOME IN LONG-TERM STUDIED PATIENTS WITH POSTTRANSFUSION
HEPATITIS C
MATSSON L; GUTIERREZ R A; DAWSON G J; LESNIEWSKI R R; MUSHAWWAR I K;
WEILAND O
DEP. INFECTIOUS DIS., KAROLINSKA INST., ROSLAGSTULL HOSP., BOX 5651,
45-114 89 STOCKHOLM, SWEDEN.
SCAND J GASTROENTEROL 26 (12). 1991. 1257-1262. CODEN: SJGRA
Full Journal Title: Scandinavian Journal of Gastroenterology
Language: ENGLISH

506/3/6 (Item 6 from file: 5)
9057009 BIOSIS Number: 93042089
SURROGATE MARKERS ARE NOT USEFUL FOR IDENTIFICATION OF HCV CARRIERS IN
CHRONIC HEMODIALYSIS PATIENTS
WILLEMS M; DE JONG G; MOSHAGE H; VERRESEN L; GOUBAU P; DESMYTER J; YAP S

H
DIV. LIVER PANCREATIC DISEASES, DEP. INTERNAL MED., UNIV. HOSP.
GASTHUISBERG, B-3000 LEUVEN, BELGIUM.

J MED VIROL 35 (4). 1991. 303-306. CODEN: JMVID
5 Full Journal Title: Journal of Medical Virology
Language: ENGLISH

6/3/7 (Item 7 from file: 5)
9046149 BIOSIS Number: 93031149
10 LEUKEMIA AND LIVER DISEASE IN CHILDHOOD CLINICAL AND HISTOLOGICAL
EVALUATION
GUIDO M; ROSSETTI F; RUGGE M; CESARO S; ANELONI V; NINFO V; ZANESCO L
DIVISIONE ANATOMIA PATOLOGICA, O.C. CITTADELLA, VIA CASA RICOVERO, 35013
CITTADELLA, ITALY.
15 TUMORI 77 (4). 1991. 319-322. CODEN: TUMOA
Full Journal Title: Tumori
Language: ENGLISH

6/3/8 (Item 8 from file: 5)
20045073 BIOSIS Number: 93030073
NUCLEOTIDE SEQUENCE OF THE GENOMIC RNA OF HEPATITIS C VIRUS ISOLATED FROM
A HUMAN CARRIER COMPARISON WITH REPORTED ISOLATES FOR CONSERVED AND
DIVERGENT REGIONS
OKAMOTO H; OKADA S; SUGIYAMA Y; KURAI K; IIZUKA H; MACHIDA A; MIYAKAWA Y;
20 MAYUMI M
IMMUNOL. DIV., JICHI MED. SCH., MINAMIKAWACHI-MACHI, TOCHIGI-KEN 329-04.
J GEN VIROL 72 (11). 1991. 2697-2704. CODEN: JGVIA
Full Journal Title: Journal of General Virology
Language: ENGLISH

30
6/3/9 (Item 9 from file: 5)
9037409 BIOSIS Number: 93022409
PREDICTION OF HEPATITIS C VIRUS INFECTIVITY IN SEROPOSITIVE AUSTRALIAN
BLOOD DONORS BY SUPPLEMENTAL IMMUNOASSAYS AND DETECTION OF VIRAL RNA
35 ALLAIN J-P; COGHLAN P J; KENRICK K B; WHITSON K; KELLER A; COOPER G J;
VALLARI D S; DELANEY S R; KUHN M C
DEP. TRANSFUSION MED., REGIONAL BLOOD TRANSFUSION CENTRE, LONG RD.,
CAMBRIDGE CB2 2PT, UK.
BLOOD 70 (2). 1991. 2462-2468. CODEN: BLOOA
40 Full Journal Title: Blood
Language: ENGLISH

6/3/10 (Item 10 from file: 5)
9033505 BIOSIS Number: 93018505
45 EVIDENCE FOR PERSISTENT HEPATITIS C VIRUS HCV INFECTION IN HEMOPHILIACS
ALLAIN J-P; DAILEY S H; LAURIAN Y; VALLARI D S; RAFOWICZ A; DESAI S M;
DEVARE S S
DEP. TRANSFUSION MED., UNIV. CAMBRIDGE, LONG ROAD, CAMBRIDGE CB2 2PT,
ENGL.
50 J CLIN INVEST 88 (5). 1991. 1672-1679. CODEN: JCINA
Full Journal Title: Journal of Clinical Investigation
Language: ENGLISH

6/3/11 (Item 11 from file: 5)

9025607 BIOSIS Number: 93010607

EFFECT OF SCREENING FOR HEPATITIS C VIRUS ANTIBODY AND HEPATITIS B VIRUS
CORE ANTIBODY ON INCIDENCE OF POST-TRANSFUSION HEPATITIS

JPN RED CROSS NON-A NON-B HEPATITIS RES GROUP

5 INQ.: K. NISHIOKA, JAPANESE RED CROSS CENTRAL BLOOD CENT., 44-1-31,
HIROO, SHIBUYA-KU, TOKYO 150, JPN.

LANCET (N AM ED) 338 (8774). 1991. 1040-1041. CODEN: LANAA

Language: ENGLISH

106/3/12 (Item 12 from file: 5)

9025347 BIOSIS Number: 93010347

PREVALENCE OF ANTIBODY OF HEPATITIS C VIRUS IN HEMODIALYSIS PATIENTS

HAYASHI J; NAKASHIMA K; KAJIYAMA W; NOGUCHI A; MOROFUJI M; MAEDA Y;

KASHIWAGI S

15 DEP. GEN MED., KYUSHU UNIV. HOSP. 71, HIGASHI-KU, FUKUOKA 812, JPN.

AM J EPIDEMIOL 134 (6). 1991. 651-657. CODEN: AJEPA

Full Journal Title: American Journal of Epidemiology

Language: ENGLISH

206/3/13 (Item 13 from file: 5)

9021176 BIOSIS Number: 93006176

INCIDENCE OF NON-A NON-B HEPATITIS AFTER SCREENING BLOOD DONORS FOR
ANTIBODIES TO HEPATITIS C VIRUS AND SURROGATE MARKERS

BARRERA J M; BRUGUERA M; ERCILLA G; SANCHEZ-TAPIAS J M; GIL M P; GIL C;
BOOSTA J; GELABERT A; RODES J; CASTILLO R

LIVER UNIT, HOSP. CLINIC I PROVINCIAL, VILLARROEL 170, 08036 BARCELONA,
SPAIN.

ANN INTERN MED 115 (8). 1991. 596-600. CODEN: AIMEA

Full Journal Title: Annals of Internal Medicine

30 Language: ENGLISH

6/3/14 (Item 14 from file: 5)

9020196 BIOSIS Number: 93005196

THE USE OF A RECOMBINANT IMMUNOBLOT ASSAY IN THE INTERPRETATION OF
ANTI-HEPATITIS C VIRUS REACTIVITY AMONG PROSPECTIVELY FOLLOWED PATIENTS
IMPLICATED DONORS AND RANDOM DONORS

ALTER H J; TEGTMEIER G E; JETT B W; QUAN S; SHIH J W; BAYER W L; POLITO A
IMMUNOL. SECT., DEP. TRANSFUS. MED., WARREN G. MAGNUSON CLIN. CENT.,
NATL. INST. HEALTH, 9000 ROCKVILLE PIKE, ROOM 1C711, BETHESDA, MD. 20892,
40SA.

TRANSFUSION (ARLNGT) 31 (8). 1991. 771-776. CODEN: TRANA

Language: ENGLISH

6/3/15 (Item 15 from file: 5)

48814506 BIOSIS Number: 42039506

DOES ANTI-HBC ALONE INCREASE THE RISK FOR HEPATOCELLULAR CARCINOMA IN
ANTI-HCV POSITIVE CIRRHOSIS?

COSTA J; SANCHEZ-TAPIAS J M; BRUIX J; BRANDAO A; BARRERA J M; RODES J
LIVER UNIT, HOSP. CLIN., UNIV. BARCELONA, SPAIN.

50 26TH MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER,
PALMA DE MALLORCA, SPAIN, SEPTEMBER 11-14, 1991. J HEPATOL (AMST) 13

(SUPPL. 2). 1991. S111. CODEN: JONEE

Language: ENGLISH

Document Type: CONFERENCE PAPER

6/3/16 (Item 16 from file: 5)
8665323 BIOSIS Number: 92130323
HEPATITIS C ANTIBODY PREVALENCE IN SAUDI ARABIAN BLOOD DONOR POPULATION
BERNVIL S S; ANDREWS V J; KARIEM A A
5 DEP. PATHOL. AND LAB. MED., KING FAISAL SPECIALIST HOSP. AND RES. CENT.,
P.O. BOX 3354, RIYADH 11211, SAUDI ARABIA.
ANN SAUDI MED 11 (5). 1991. 563-567. CODEN: ANSME
Language: ENGLISH

106/3/17 (Item 17 from file: 5)
8665316 BIOSIS Number: 92130316
PREVALENCE OF ANTIBODIES TO HEPATITIS C VIRUS IN SAUDI AND EXPATRIATE
WOMEN IN RIYADH SAUDI ARABIA
FAKUNLE Y M; AL-MOFARREH M; AL-GHREIMIL M S; IDREES Y B; EL-DREES A Z;
18L-KARAMANY W; EZZAT H O
DEP. MED., P.O. BOX 24869, RIYADH 11456, SAUDI ARABIA.
ANN SAUDI MED 11 (5). 1991. 494-496. CODEN: ANSME
Language: ENGLISH

206/3/18 (Item 18 from file: 5)
8628225 BIOSIS Number: 92093225
PREVALENCE OF ANTIBODY TO HEPATITIS C VIRUS IN PREGNANT TAIWANESE
LIN H-H; HSIEH R-P; WANG C-Y; CHEN P-J; CHEN D-S
DEP. OBSTETRICS GYNECOL., NATIONAL TAIWAN UNIV. HOSPITAL, NO. 1, CHANG-TE
2STREET, TAIPEI, TAIWAN 10016.
J FORMOSAN MED ASSOC 90 (5). 1991. 476-479. CODEN: TIHHA
Full Journal Title: Journal of the Formosan Medical Association
Language: ENGLISH

306/3/19 (Item 19 from file: 5)
8624135 BIOSIS Number: 92089135
MINIMAL ROLE OF HEPATITIS B VIRUS IN POSTTRANSFUSION NON-A NON-B
HEPATITIS IN TAIWAN A STUDY BY POLYMERASE CHAIN REACTION
WANG J-T; SHEU J-C; LIN J-T; SHIH L-N; CHEN D-S; WANG T-H
35 DEP. INTERNAL MED., NATIONAL TAIWAN UNIV. HOSPITAL, NO. 1, CHANG-TE ST,
TAIPEI, TAIWAN.
J FORMOSAN MED ASSOC 90 (5). 1991. 471-475. CODEN: TIHHA
Full Journal Title: Journal of the Formosan Medical Association
Language: ENGLISH

40
6/3/20 (Item 20 from file: 5)
8587899 BIOSIS Number: 92052899
ALANINE AMINOTRANSFERASE GAMMA GLUTAMYLTRANSFERASE ANTIBODIES TO
HEPATITIS B CORE ANTIGEN AND ANTIBODIES TO HEPATITIS C VIRUS IN BLOOD DONOR
45SCREENING A PROSPECTIVE STUDY IN FINLAND
EBELING F
FINNISH RED CROSS BLOOD TRANSFUSION SERV., KIVIHAANTIE 7, SF-00310
HELSINKI, FINLAND.
VOX SANG 60 (4). 1991. 219-224. CODEN: VOSAA
50 Full Journal Title: Vox Sanguinis
Language: ENGLISH

6/3/21 (Item 21 from file: 5)
8577685 BIOSIS Number: 92042685

PREVALENCE OF ANTIBODY AGAINST THE CORE PROTEIN OF HEPATITIS C VIRUS IN
PATIENTS WITH HEPATOCELLULAR CARCINOMA

WATANABE Y; HARADA S; SAITO I; MIYAMURA T
LAB. HEPATITIS VIRUSES II, DEP. ENTEROVIRUSES, NATIONAL INST. HEALTH,
8-10-35 KAMIOSAKI, SHINAGAWA-KU, TOKYO 141, JPN.
INT J CANCER 48 (3). 1991. 340-343. CODEN: IJCNA
Full Journal Title: International Journal of Cancer
Language: ENGLISH

106/3/22 (Item 22 from file: 5)

8577153 BIOSIS Number: 92042153

SERODIAGNOSIS OF HEPATITIS C VIRUS HCV INFECTION WITH AN HCV CORE PROTEIN
MOLECULARLY EXPRESSED BY A RECOMBINANT BACULOVIRUS

CHIBA J H O; MATSUURA Y; WATANABE Y; KATAYAMA T; KIKUCHI S; SAITO I;
MIYAMURA T

DEP. BIOLOGICAL SCI. TECHNOL., SCI. UNIV. TOKYO, 2641 YAMAZAKI, NODA-SHI,
CHIBA 278, JPN.

PROC NATL ACAD SCI U S A 88 (11). 1991. 4641-4645. CODEN: PNASA

Full Journal Title: Proceedings of the National Academy of Sciences of
the United States of America

Language: ENGLISH

6/3/23 (Item 23 from file: 5)

8551892 BIOSIS Number: 92016092

25 PREVALENCE OF ANTIBODY TO HEPATITIS C VIRUS IN A BLOOD DONOR POPULATION
RICHARDS C A; HOLLAND P; KURAMOTO K; DOUVILLE C; RANDELL R

SACRAMENTO MED. FOUND., BLOOD CENT., CENT. BLOOD RES., 1625 STOCKTON
BLVD., SACRAMENTO, CALIF. 95816-7089, USA.

TRANSFUSION (ARLNGT) 31 (2). 1991. 109-113. CODEN: TRANA

30 Language: ENGLISH

6/3/24 (Item 24 from file: 5)

8541118 BIOSIS Number: 9206118

CHRONIC EVOLUTION OF ACUTE HEPATITIS B THE SIGNIFICANCE OF SIMULTANEOUS
REINFECTIONS WITH HEPATITIS C AND D

KROGSGAARD K; WANTZIN P; MATHIESEN L; RING-LARSEN H; COPENH HEPATITIS
ACUTE PROG

DEP. INFECT. DIS. 144, HVIDOVRE HOSP., 2650 HVIDOVRE, DEN.

SCAND J GASTROENTEROL 26 (3). 1991. 275-280. CODEN: SJGRA

40 Full Journal Title: Scandinavian Journal of Gastroenterology

Language: ENGLISH

6/3/25 (Item 25 from file: 5)

8427311 BIOSIS Number: 41111311

45 TESTING OF BLOOD DONORS FOR ANTIBODY TO HCV THE HAWAII USA EXPERIENCE
FROHLICH J

BLOOD BANK HAWAII, 2043 DILLINGHAM BLVD., HONOLULU, HAWAII 96819.

HAWAII MED J 50 (7). 1991. 231-232, 253. CODEN: HUMJA

Full Journal Title: Hawaii Medical Journal

50 Language: ENGLISH

6/3/26 (Item 26 from file: 5)

8356616 BIOSIS Number: 41040616

PATTERNS OF ANTIBODY RESPONSE TO HEPATITIS C VIRUS HCV IN CHRONIC NON-A

NON-A NANO HEPATITIS

PITRAK D L; NELSON M; WILEY T; HEYNE C; HOLZER T; KEITH R; LAYDEN T J
DEP. MED., UNIV. ILL. AT CHICAGO, ABBOTT LAB., N. CHICAGO, ILL.

JOINT MEETING OF THE ASSOCIATION OF AMERICAN PHYSICIANS, THE AMERICAN
SOCIETY FOR CLINICAL INVESTIGATION, AND THE AMERICAN FEDERATION FOR
CLINICAL RESEARCH, SEATTLE, WASHINGTON, USA, MAY 3-6, 1991. CLIN RES 39
(2). 1991. 169A. CODEN: CLREA

Language: ENGLISH

Document Type: CONFERENCE PAPER

10

6/3/27 (Item 27 from file: 5)

8145719 BIOSIS Number: 91066719

PREVALENCE OF HEPATITIS C IN SOUTH AFRICA DETECTION OF ANTI-HCV IN RECENT
AND STORED SERUM

15 ELLIS L A; BROWN D; CONRADIE J D; PATERSON A; SHER R; MILLO J;
THEODOSSIADOU E; DUSHEIKO G M

ROYAL FREE HOSPITAL SCHOOL MEDICINE, DEP. MEDICINE, HAMPSTEAD, LONDON NW3
200, UK.

J MED VIROL 32 (4). 1990. 249-251. CODEN: JMVID

20 Full Journal Title: Journal of Medical Virology

Language: ENGLISH

6/3/28 (Item 28 from file: 5)

8089002 BIOSIS Number: 91010002

25 HUMAN IMMUNODEFICIENCY VIRUS HIV INFECTION SEXUALLY TRANSMITTED DISEASES
AND HIV-ANTIBODY TESTING PRACTICES IN BELGIAN PROSTITUTES

MAK R; PLUM J; VAN RENTERGHEM L

DEP. HYGIENE AND SOCIAL MED., UNIV. HOSP., BLOCK A, PINTELAAN 185, 2000
GHENT, BELGIUM.

30 GENITOURIN MED 66 (5). 1990. 337-341. CODEN: GEMEE

Full Journal Title: Genitourinary Medicine

Language: ENGLISH

6/3/29 (Item 29 from file: 5)

35712772 BIOSIS Number: 90090379

CHARACTERIZATION OF CARDIAC ANGIOTENSIN CONVERTING ENZYME ACE AND IN-VIVO
INHIBITION FOLLOWING ORAL QUINAPRIL TO RATS

FABRIS B; YAMADA H; CUBELA R; JACKSON B; MENDELSON F A O; JOHNSON C I
UNIV. OF MELBOURNE, DEP. OF MED., AUSTIN HOSP., HEIDELBERG, VICTORIA,

40084 AUST.

BR J PHARMACOL 100 (3). 1990. 651-655. CODEN: BJPCB

Full Journal Title: British Journal of Pharmacology

Language: ENGLISH

456/3/30 (Item 30 from file: 5)

7712685 BIOSIS Number: 90090292

QUANTITATIVE DETERMINATION OF BETA EXOTOXIN OF BACILLUS-THURINGIENSIS IN
INSECTICIDE BIOPREPARATIONS

EFIMTSEV E I; BUROV G P; SOLOMIN A A

50 MOSC. FOR.-TECH. INST., MOSCOW, USSR.

BIOL NAUKI (MOSC) 0 (2). 1990. 119-126. CODEN: BINKB

Full Journal Title: Biologicheskii NAUKI (Moscow)

Language: RUSSIAN

6/3/31 (Item 31 from file: 5)
7701140 BIOSIS Number: 90078747
EPIZOOTIOLOGY OF AMBLYOSPORA-CONNECTICUS MICROSPORIDA IN FIELD
POPULATIONS OF THE SALTMARSH MOSQUITO AEDES-CANTATOR AND THE CYCLOPOID
BOREPOD ACANTHOCYCLOPS-VERNALIS
ANDREADIS T G
DEP. ENTOMOL., CONNECTICUT AGRICULTURAL EXPERIMENT STATION, P.O. BOX
1106, NEW HAVEN, CONN. 06504.
J PROTOZOO 37 (3). 1990. 174-182. CODEN: JPROA
10 Full Journal Title: Journal of Protozoology
Language: ENGLISH

6/3/32 (Item 32 from file: 5)
7640935 BIOSIS Number: 90018542
15 THE BASIS OF HIGH-INTENSITY ULTRASOUND PHENOMENA DURING INJECTION OF
CONTRAST MEDIA
STAUDACHER T; PREY N; SONNTAG W; STOETER P
NEURORADIOLOGISCHE ABTEILUNG, ST. ELISABETHEN-KRANKENHAUS, D-7980
RAVENSBURG, GER.
20 RADIOLOGE 30 (3). 1990. 124-129. CODEN: RDLGB
Full Journal Title: Radiologe
Language: GERMAN

6/3/33 (Item 33 from file: 5)
27413187 BIOSIS Number: 89064206
EPIDEMIOLOGY OF HEPATITIS C VIRUS A PRELIMINARY STUDY IN VOLUNTEER BLOOD
DONORS
STEVENS C E; TAYLOR P E; PINDYCK J; CHOO Q-L; BRADLEY D W; KUO G;
HOUGHTON M
30 NEW YORK BLOOD CENT., 310 E. 67TH ST., NEW YORK, N.Y. 10021.
JAMA (J AM MED ASSOC) 263 (1). 1990. 49-53. CODEN: JAMAA
Full Journal Title: JAMA (Journal of the American Medical Association)
Language: ENGLISH

356/3/34 (Item 34 from file: 5)
7306982 BIOSIS Number: 89038001
DETECTION OF ANTIBODY TO HEPATITIS C VIRUS IN PROSPECTIVELY FOLLOWED
TRANSFUSION RECIPIENTS WITH ACUTE AND CHRONIC NON-A NON-B HEPATITIS
ALTER H J; PURCELL R H; SHIH J W; MELPOLDER J C; HOUGHTON M; CHOO Q-L;
40 KUO G
DEP. TRANSFUS. MED., BLDG. 10, RM. 5D 56, NATL. INST. HEALTH, BETHESDA,
MD. 20892.
N ENGL J MED 321 (22). 1989. 1494-1500. CODEN: NEJMA
Full Journal Title: New England Journal of Medicine
45 Language: ENGLISH

6/3/35 (Item 35 from file: 5)
7376946 BIOSIS Number: 89027965
PREVALENCE OF ANTIBODIES TO HEPATITIS C VIRUS IN ITALIAN PATIENTS WITH
HEPATOCELLULAR CARCINOMA
COLOMBO M; CHOO Q L; DEL NINNO E; DIOSGUARDI N; KUO G; DONATO M F;
TOMMASINI M A; HOUGHTON M
INST. INTERNAL MED., UNIV. MILAN, VIA PACE 9, 20122 MILAN, ITALY.
LANCET 2 (8670). 1989. 1006-1008. CODEN: LANCA

Full Journal Title: Lancet
Language: ENGLISH

6/3/36 (Item 36 from file: 5)
5004213 BIOSIS Number: 87064734
HEPATITIS B VIRUS DNA IN THE SERUM OF SARDINIAN BLOOD DONORS NEGATIVE FOR
THE HEPATITIS B SURFACE ANTIGEN
LAI M E; FARCI P; FIGUS A; BALESTRIERI A; ARNONE M; VYAS G N
TRANSFUS. RES. PROGRAM, DEP. LAB. MED., UNIV. CALIF., SAN FRANCISCO,
10ALIF. 94143-0100, USA.
BLOOD 73 (1). 1989. 17-19. CODEN: BLOOA
Full Journal Title: Blood
Language: ENGLISH

156/3/37 (Item 37 from file: 5)
6000921 BIOSIS Number: 34083228
COMPARISON OF SURROGATE MARKERS FOR NANB HEPATITIS IN TRANSFUSED AND
NON-TRANSFUSED INDIVIDUALS
CONWAY M; NG A; BLANDA E; KILLIGREW B; EASTMAN C
20 AM. RED CROSS BLOOD SERV., CENTRAL OHIO REGION, COLUMBUS, OHIO.
40TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF BLOOD BANKS, NOVEMBER
7-12, 1987. TRANSFUSION (PHILA) 27 (6). 1987. 532. CODEN: TRANA
Language: ENGLISH
Document Type: CONFERENCE PAPER

25
6/3/38 (Item 38 from file: 5)
5883041 BIOSIS Number: 94015406
MODIFICATIONS IN TIME OF THE ANTI-HBC IGM RESPONSE IN A CASE-LIST OF HBV
HEPATITIS DIAGNOSTIC IMPLICATIONS
30 CREMONI L; BUFFA D; SAUCCO F; BONGETTA R; AROSIO M; D'AMICO P
PRESIDIO MULTIZONALE DELLA U.S.S.L. 64-MONZA.
BOLL. IST SIEROTER MILAN 65 (5). 1986 (1987). 430-435. CODEN: BISM
Full Journal Title: Bollettino dell'Istituto Sieroterapico Milanese
Language: ITALIAN

35
6/3/39 (Item 39 from file: 5)
5430106 BIOSIS Number: 82082909
CUTOFF LEVELS OF IMMUNOGLOBULIN M ANTIBODY AGAINST VIRAL CORE ANTIGEN FOR
DIFFERENTIATION OF ACUTE CHRONIC AND PAST HEPATITIS B VIRUS INFECTIONS
40 GERLICH W H; UY A; LAMBRECHT F; THOMSEN R
DEP. MED. MICROBIOL., UNIV. GOETTINGEN, D-3440 GOETTINGEN, FEDERAL
REPUBLIC OF GER.
J CLIN MICROBIOL 24 (2). 1986. 288-293. CODEN: JCMID
Full Journal Title: Journal of Clinical Microbiology
45 Language: ENGLISH

6/3/40 (Item 40 from file: 5)
5272919 BIOSIS Number: 81041226
A STUDY ON SO-CALLED NOVEL INCLUSION BODY IN HUMAN HEPATOCYTE
50 TANAKA K; MORI W; KAWANO N
DEP. PATHOL., FAC. MED., UNIV. TOKYO, 7-3-1, HONGO, BUNKYO-KU, TOKYO 113,
JPN.
ACTA PATHOL JPN 35 (5). 1985. 1141-1150. CODEN: APJAA
Full Journal Title: Acta Pathologica Japonica

Language: ENGLISH

6/3/41 (Item 41 from file: 5)
4969135 BIOSIS Number: 80096446
5 DELTA SYSTEM IN PATIENTS WITH ACUTE OR CHRONIC HEPATITIS B VIRUS
INFECTION
CHIRCU L V; MARINUCCI G; DI GIACOMO C; MORGANTI D; ZANZOGU S; CILLI A M;
SETTEMBRE G; GALLI C; SONEGO G; IANNICELLI G
VIA DI TRASONE 58/A, 00199 ROMA, ITALY.
10 ITAL J GASTROENTEROL 17 (4). 1985. 195-199. CODEN: ITJGD
Full Journal Title: Italian Journal of Gastroenterology
Language: ENGLISH

6/3/42 (Item 42 from file: 5)
15802308 BIOSIS Number: 79044623
ETIOLOGY OF ACUTE SPORADIC HEPATITIS IN ADULTS IN KENYA
GREENFIELD C; WANKYA B M; SHAH M V; TUKEI P; GALPIN S; JOWETT T P; THOMAS
H C; KARAYIANNIS P
DEP. MED., ROYAL FREE HOSP. SCH. MED., ROWLAND HILL ST., LONDON NW3 2PF,
ENGLAND.
J MED VIROL 14 (4). 1984. 357-362. CODEN: JMVID
Full Journal Title: Journal of Medical Virology
Language: ENGLISH

256/3/43 (Item 43 from file: 5)
4363866 BIOSIS Number: 77039193
NON-A NON-B HEPATITIS A PROSPECTIVE STUDY OF A HEMO DIALYSIS OUTBREAK
WITH EVALUATION OF A SEROLOGIC MARKER IN PATIENTS AND STAFF
GITNICK G; WEISS S; OVERBY L R; LING C-M; CHAIREZ R; PARSA K
30 DEP. MED., C-LOT, ROOM 112, UCLA CENTER HEALTH SCI., LOS ANGELES, CALIF.
90024.
HEPATOLOGY (BALTIMORE) 3 (5). 1983. 625-630. CODEN: HPTLD
Full Journal Title: HEPATOLOGY (Baltimore)
Language: ENGLISH

35
6/3/44 (Item 44 from file: 5)
4122686 BIOSIS Number: 76072537
ANTI HEPATITIS B CORE IMMUNO GLOBULIN M IN THE SEROLOGIC EVALUATION OF
HEPATITIS B VIRUS INFECTION AND SIMULTANEOUS INFECTION WITH TYPE B DELTA
4088 ANT AND NON-A NON-B VIRUSES
PERRILLO R P; CHAU K H; OVERBY L R; DECKER R H
MED. SERVICE, VETERANS ADM. MED. CENT., ST. LOUIS, MO 63125.
GASTROENTEROLOGY 85 (1). 1983. 163-167. CODEN: GASTA
Full Journal Title: Gastroenterology
45 Language: ENGLISH

6/3/45 (Item 45 from file: 5)
3720964 BIOSIS Number: 74020827
ACUTE VIRAL HEPATITIS A HEPATITIS B AND HEPATITIS NON-A NON-B IN
50 STOCKHOLM SWEDEN IN THE 1950S AND 1970S A COMPARISON
WEILAND O; BERG J V R; BJORVATN B; FLEHMIG B; LUNDBERGH P
DEP. INFECTIOUS DISEASES, KAROLINSKA INST., ROSLAGSTULL HOSP., BOX 5901,
S-114 89 STOCKHOLM, SWED.
INFECTION 9 (6). 1981 (RECD. 1982). 268-274. CODEN: IFTNA

Full Journal Title: Infection
Language: ENGLISH

6/3/46 (Item 46 from file: 5)

5658641 BIOSIS Number: 73051008

NON-A NON-B HEPATITIS VIRUS IDENTIFICATION OF A CORE ANTIGEN ANTIBODY
SYSTEM THAT CROSS REACTS WITH HEPATITIS B CORE ANTIGEN AND ANTIBODY
TREPO C; VITVITSKI L; HANTZ O
PAVILLON H, HOPITAL E. HERRIOT, 69374 LYON CEDEX 2, FRANCE.

10 J MED VIROL 8 (1), 1981. 31-48. CODEN: JMVID

Full Journal Title: Journal of Medical Virology
Language: ENGLISH

6/3/47 (Item 47 from file: 5)

15655210 BIOSIS Number: 73047577

ACUTE VIRAL HEPATITIS TYPES A D AND NON-A NON-B A PROSPECTIVE STUDY OF
THE EPIDEMIOLOGICAL LABORATORY AND PROGNOSTIC ASPECTS IN 280 CONSECUTIVE
CASES

WEILAND O; BERG J V R; FLEHMIG R; LINDH G; LUNDBERGH P
20 ROSLAGSTULL HOSP., BOX 5901, S-11489 STOCKHOLM, SWEDEN.
SCAND J INFECT DIS 13 (4), 1981. 247-255. CODEN: SJIDB

Full Journal Title: Scandinavian Journal of Infectious Diseases
Language: ENGLISH

256/3/48 (Item 48 from file: 5)

3334261 BIOSIS Number: 71056660

NON-A NON-B HEPATITIS IDENTIFICATION OF 2 ANTIGENS ASSOCIATED WITH A
HEPATITIS B-LIKE VIRION AND CROSS REACTING WITH HEPATITIS B CORE AND
HEPATITIS B E ANTIGENS

30 TREPO C; VITVITSKI L; HANTZ O; GRIMAUD J-A

I.N.S.E.R.M. U. 45, C.N.R.S. LP 05440, PAVILLON H, HOP. E. HERRIOT, 69374
LYON.

C R WEDD SEANCES ACAD SCI SER D SCI NAT 290 (4), 1980. 343-346.
CODEN: CHDDA

35 Full Journal Title: Comptes Rendus Hebdomadaires des Seances de
l'Academie des Sciences Serie D Sciences Naturelles
Language: FRENCH

6/3/49 (Item 1 from file: 155)

407999892 92137892

Prevalence of antibodies to hepatitis C virus among patients with
cryptogenic chronic hepatitis and cirrhosis [see comments]

Jeffers LJ; Hasan F; De Medina M; Reddy R; Parker T; Silva M; Mendez L;
Schiff ER; Manns M; Houghton M

45 Division of Hepatology, University of Miami School of Medicine, Florida
33101.

Hepatology (UNITED STATES) Feb 1992, 15 (2) p187-90, ISSN 0270-9129
Journal Code: GBZ

Comment in Hepatology 1992 Feb;15(2):350-3

50 Languages: ENGLISH

Document type: JOURNAL ARTICLE

6/3/50 (Item 2 from file: 155)

07994927 92132997

Seroepidemiology of viral infections among intravenous drug users in northern California.

Zeldis JD; Jain S; Kuramoto IK; Richards C; Sazama K; Samuels S; Holland PV; Flynn N

5 Department of Internal Medicine, University of California, Davis, School of Medicine.

West J Med (UNITED STATES) Jan 1992, 156 (1) p30-5, ISSN 0093-0415

Journal Code: XNS

Contract/Grant No.: K08-HL01917; R01-DA05250

10 Languages: ENGLISH

Document type: JOURNAL ARTICLE

6/3/51 (Item 3 from file: 155)

07988820 92126820

15 An autoantibody cross-reactive to hepatitis C virus core and a host nuclear antigen.

Mishiro S; Takeda K; Hoshi Y; Yoshikawa A; Gotanda T; Itoh Y

Institute of Immunology, Tokyo, Japan.

Autoimmunity (SWITZERLAND) 1991, 10 (4) p269-73, ISSN 0891-6934

20 Journal Code: A5H

Languages: ENGLISH

Document type: JOURNAL ARTICLE

6/3/52 (Item 4 from file: 155)

207984537 92122537

[Infection of hepatitis C virus in patients with chronic renal failure undergoing hemodialysis therapy and staff members]

Miyasaka M

2nd Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan.

Nippon Jinzo Gakkai Shi (JAPAN) Oct 1991, 33 (10) p989-99, ISSN

0385-2385 Journal Code: KMK

Languages: JAPANESE Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

35

6/3/53 (Item 5 from file: 155)

07982707 92120707

[Massive and multi-transfusions in polytraumatized patients: long-term serologic markers of hepatitis B, hepatitis C and AIDS]

40 Massive- und Multitransfusion bei polytraumatisierten Patienten:

Langfristige serologische Befunde zu Hepatitis B, Hepatitis C und AIDS.

Schneck HJ; Dobler G; Hundelshausen B; Nathrath M; Drescher M

Institut für Anaesthesiologie, Technischen Universität München.

Infusionstherapie (SWITZERLAND) Oct 1991, 18 (5) p248-55, ISSN

45011-6956 Journal Code: GPC

Languages: GERMAN Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

6/3/54 (Item 6 from file: 155)

507959465 92097465

Hepatitis B virus markers and antibodies to hepatitis C virus in Japanese patients with hepatocellular carcinoma.

Yuki M; Hayashi N; Kasahara A; Hagiwara H; Katayama K; Fusamoto H; Kamada T.

First Department of Medicine, Osaka University Medical School, Japan.
Dig Dis Sci (UNITED STATES) Jan 1992, 37 (1) p65-72, ISSN 0163-2116
Journal Code: EAD
Languages: ENGLISH
5 Document type: JOURNAL ARTICLE

6/3/55 (Item 7 from file: 155)
07958601 92096601
IgM antibody response in acute hepatitis C viral infection.
10 Clemens JM; Taskar S; Chau K; Vallari D; Shih JW; Alter MJ; Schleicher JD
; Mims LT
Abbott Laboratories, Abbott Park, IL 60064.
Blood (UNITED STATES) Jan 1 1992, 79 (1) p169-72, ISSN 0006-4971
Journal Code: A80
15 Languages: ENGLISH
Document type: JOURNAL ARTICLE

6/3/56 (Item 8 from file: 155)
07950920 92088920
20 Consistently normal CD4+, CD8+ levels in haemophilic boys only treated
with a virally safe factor VIII concentrate (BPL 8Y).
Evans JA; Pasi KJ; Williams MD; Hill FG
Department of Haematology, Children's Hospital, Birmingham.
Br J Haematol (ENGLAND) Nov 1991, 79 (3) p457-61, ISSN 0007-1048
25 Journal Code: AX0
Languages: ENGLISH
Document type: JOURNAL ARTICLE

6/3/57 (Item 9 from file: 155)
307944308 92082300
Decrease in reported posttransfusion hepatitis. Contributions of donor
screening for alanine aminotransferase and antibodies to hepatitis B core
antigen and changes in the general population.
Chambers LA; Popovsky MA
35 Department of Pathology, Charles A. Dana Research Institute, Beth Israel
Hospital, Boston, MA 02115.
Arch Intern Med (UNITED STATES) Dec 1991, 151 (12) p2445-8, ISSN
0003-9926. Journal Code: 7FS
Languages: ENGLISH
40 Document type: JOURNAL ARTICLE

6/3/58 (Item 10 from file: 155)
07905494 92043494
Demographic features of sporadic acute hepatitis as determined by viral
45 hepatitis markers.
Ichhpujani RL; Riley IW; Duggal L; Kumari S; Gupta PS; Sehgal S
National Institute of Communicable Diseases, Delhi, India.
J Commun Dis (INDIA) Jun 1991, 23 (2) p138-43, ISSN 0019-5138
Journal Code: IBN
50 Languages: ENGLISH
Document type: JOURNAL ARTICLE

6/3/59 (Item 11 from file: 155)
07878961 92016961

Effect of screening for hepatitis C virus antibody and hepatitis B virus core antibody on incidence of post-transfusion hepatitis. Japanese Red Cross Non-A, Non-B Hepatitis Research Group.

Lancet Oct 26 1991, 338 (8774) p1040-1, ISSN 0023-7507

Journal Code: L08

Languages: ENGLISH

Document type: CLINICAL TRIAL; JOURNAL ARTICLE; MULTICENTER STUDY

6/3/60 (Item 12 from file: 155)

107875081 92013081

Identification of an immunodominant B cell epitope on the hepatitis C virus nonstructural region defined by human monoclonal antibodies.

Carino A; Mondelli MU

Istituto di Clinica delle Malattie Infettive, I.R.C.C.S. Policlinica San Matteo, University of Pavia, Italy.

J Immunol Oct 15 1991, 147 (8) p2692-6, ISSN 0022-1767

Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

20

6/3/61 (Item 13 from file: 155)

07841998 91360998

[Anti-HBc determination in blood donors in Sao Paulo: should this test be adopted in Brazil?]

25 Pesquisa de anti-HBc em doadores de sangue em Sao Paulo: devera esse teste ser adotado pelo Brasil?

Wendel S; Luzzi JR; Russo C; de Cassia R; Fontao L; Ghaname J
Bancos de Sangue, Hospitais Sirio-Libanês, Sao Paulo.

Rev Paul Med Mar-Apr 1991, 109 (2) p77-83, ISSN 0035-0362

Journal Code: BZ5

Languages: PORTUGUESE Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

6/3/62 (Item 14 from file: 155)

307831354 91350354

[HCV antibody test methods and patterns of antibody response]

Yahagi N; Kitsugi K

Ortho Diagnostic Systems K. K., Tokyo.

Rinsho Byori Jun 1991, 39 (6) p578-85, ISSN 0047-1860

Journal Code: KIV

Languages: JAPANESE Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

6/3/63 (Item 15 from file: 155)

407831353 91350353

[Symposium: Current evaluation of diagnostic methods on viral hepatitis type C and consequent clinical features]

Ohta Y; Tsuji T

3rd Department of Internal Medicine, Ehime University School of Medicine.

50 Rinsho Byori Jun 1991, 39 (6) p575-7, ISSN 0047-1860 Journal Code: KIV

Languages: JAPANESE Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

- 6/3/64 (Item 16 from file: 155)
07614011 91333011
Hog cholera virus: molecular composition of virions from a pestivirus.
Thiel HJ; Stark R; Weiland E; Rumenapf T; Meyers G
5 Federal Research Centre for Virus Diseases of Animals, Tübingen, Federal Republic of Germany.
J Virol Sep 1991, 65 (9) p4705-12, ISSN 0022-538X Journal Code: KCV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
- 10 6/3/65 (Item 17 from file: 155)
07801630 91320630
Hepatitis C virus antibodies in high-risk Saudi groups.
Bahakim H; Bakir TM; Arif M; Ramia S
15 Department of Pediatrics, College of Medicine, King Saud University, Riyadh, Saudi Arabia.
Vox Sang 1991, 60 (3) p162-4, ISSN 0042-9007 Journal Code: XLI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
- 20 6/3/66 (Item 18 from file: 155)
07722916 91241916
Hepatitis C virus infection in haemodialysis patients.
Roger SD; Crewe E; Cunningham A; Harris DC
25 Renal Unit, Westmead Hospital, Sydney, NSW, Australia.
Aust N Z J Med Feb 1991, 21 (1) p22-4, ISSN 0004-8291
Journal Code: 949
Languages: ENGLISH
Document type: JOURNAL ARTICLE
- 30 6/3/67 (Item 19 from file: 155)
07718818 91237818
Expression of processed core protein of hepatitis C virus in mammalian cells.
35 Harada B; Watanabe Y; Takeuchi K; Suzuki T; Katayama T; Takebe Y; Saito I; Miyamura T
Department of Medical Entomology, National Institute of Health, Tokyo, Japan.
J Virol Jun 1991, 65 (6) p3015-21, ISSN 0022-538X Journal Code: KCV
40 Languages: ENGLISH
Document type: JOURNAL ARTICLE
- 6/3/68 (Item 20 from file: 155)
07692601 91211601
45 Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues, and semen for evidence of hepatitis B and hepatitis C.
MMWR Morb Mortal Wkly Rep Apr 19 1991, 40 RR 4 p1-17, ISSN 0149-2195
Journal Code: NE8
50 Languages: ENGLISH
Document type: GUIDELINE; JOURNAL ARTICLE
- 6/3/69 (Item 21 from file: 155)
07659925 91170925

[Evaluation of hepatitis B virus markers for surrogate testing of hepatitis C]

Ohto H; Nomura H; Ohmura K; Ishijima A; Okazaki S
Blood Transfusion Service, Fukushima Medical College.
5 Rinsho Byori Jan 1991, 39 (1) p14-7, ISSN 0047-1860 Journal Code:
KIV

Languages: JAPANESE Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE English Abstract

106/3/70 (Item 22 from file: 155)

07597741 91116741

[Expression of hepatitis B virus (HBV) markers in chronic liver disease positive for antibody to hepatitis C virus (HCV)]

Yuki N; Hayashi N; Kasahara A; Hagiwara H; Katayama K; Fusamoto H; Kato H
10 Masuzawa M; Kamada T

First Department of Medicine, Osaka University School of Medicine.

Nippon Shokakibyo Gakkai Zasshi Nov 1990, 87 (11) p2466-72, ISSN
0446-6586 Journal Code: KJY

Languages: JAPANESE Summary Languages: ENGLISH
20 Document type: JOURNAL ARTICLE English Abstract

6/3/71 (Item 23 from file: 155)

07587949 91106949

Hepatic histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis.

Davies GE; Portmann BC; O'Grady JG; Aldis PM; Chaggar K; Alexander GJ; Williams R

Liver Unit, King's College School of Medicine and Dentistry, Denmark Hill, London, United Kingdom.

Hepatology Jan 1991, 13 (1) p150-7, ISSN 0270-9139 Journal Code:
GBZ

Languages: ENGLISH
Document type: JOURNAL ARTICLE

35

6/3/72 (Item 24 from file: 155)

07577194 91096194

Low overlap between anti-HCV and anti-HBc in Japanese [letter]

Ohto H; Nomura H; Ohmura K; Ishijima A; Okazaki S

40 Transfusion Jan 1991, 31 (1) p88-9, ISSN 0041-1132 Journal Code:
WDN

Languages: ENGLISH
Document type: LETTER

456/3/73 (Item 25 from file: 155)

07529780 91048780

Prevalence of anti-HCV in Norwegian blood donors with anti-HBc or increased ALT levels.

Hatland G; Skaug K; Larsen J; Maland A; Stromme JH; Storvold O

50 Department of Immunology, Ullevaal Hospital, Oslo, Norway.

Transfusion Nov-Dec 1990, 30 (9) p776-9, ISSN 0041-1132

Journal Code: WDN

Languages: ENGLISH
Document type: JOURNAL ARTICLE

6/3/74 (Item 26 from file: 155)
07513776 91032776
Hepatitis A, B, C, D and E viruses: structure of their genomes and general properties.
5 Valenzuela P
Chiron Research Laboratories, Chiron Corporation, Emeryville, Ca 94608.
Gastroenterol Jpn Sep 1990, 25 Suppl 2 p62-71, ISSN 0435-1339
Journal Code: FHY
Languages: ENGLISH
10 Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

6/3/75 (Item 27 from file: 155)
07505517 91024517
Study of preneoplastic changes of liver cells by immunohistochemical and molecular hybridization techniques.
Govindarajan S; Conrad A; Lim B; Valinluck B; Kim AM; Schmid P
Liver Unit, Rancho Los Amigos Medical Center, University of Southern California.
Arch Pathol Lab Med Oct 1990, 114 (10) p1042-5, ISSN 0003-9985
20 Journal Code: 79Z
Languages: ENGLISH
Document type: JOURNAL ARTICLE

6/3/76 (Item 28 from file: 155)
07477101 90384101
Hepatitis C infection in two urban hemodialysis units.
Jeffers LJ; Perez GO; de Medina MD; Ortiz-Interian CJ; Schiff ER; Reddy KR; Jimenez M; Bourgoignie JJ; Vaamonde CA; Duncan R; et al
Department of Medicine, University of Miami School of Medicine, 30606, Miami, Florida.
Kidney Int Aug 1990, 38 (2) p320-2, ISSN 0085-2538 Journal Code: KVB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

35 6/3/77 (Item 29 from file: 155)
07463822 90370822
Hepatitis C virus infection is associated with the development of hepatocellular carcinoma.
40 Saito I; Miyamura T; Ohbayashi A; Harada H; Katayama T; Kikuchi S; Watanabe Y; Koi S; Onji M; Ohta Y; et al
Department of Enteroviruses, National Institute of Health, Tokyo, Japan.
Proc Natl Acad Sci U S A Sep 1990, 87 (17) p6547-9, ISSN 0027-8424
Journal Code: PVB
45 Languages: ENGLISH
Document type: JOURNAL ARTICLE

6/3/78 (Item 30 from file: 155)
07397336 90304336
50 Prevalence of hepatitis C virus antibody in a cohort of hemophilia patients [see comments]
Brettler DB; Alter HJ; Dienstag JL; Forsberg AD; Levine PH
Medical Center of Central Massachusetts-Memorial, Worcester 01605.
Blood Jul 1 1990, 76 (1) p254-6, ISSN 0006-4971 Journal Code: ABB

Contract/Grant No.: MCI-252002-01
Comment in Blood 1991 Mar 15;77(6):1399-400
Languages: ENGLISH
Document type: JOURNAL ARTICLE

5
6/3/79 (Item 31 from file: 155)
07364250 90271250

Prevalence of hepatitis B and C viral markers in black and white patients with hepatocellular carcinoma in the United States [see comments]
10 Yu MC; Tong MJ; Coursaget P; Ross RK; Govindarajan S; Henderson BE
Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles 90033-0800.
J Natl Cancer Inst Jun 20 1990; 82 (12) p1030-41, ISSN 0027-0074
Journal Code: J9J

15 Contract/Grant No.: CA-17054
Comment in J Natl Cancer Inst 1990 Jun 20;82(12):286-7
Languages: ENGLISH
Document type: JOURNAL ARTICLE

206/3/80 (Item 32 from file: 155)
07350600 90257600

Intrahepatic expression of HBcAg and delta antigen in anti-HBe positive HBsAg carriers with acute exacerbation or chronic active liver disease.
Chu CM; Liaw YF; Sheen IS; Chen TJ
25 Liver Unit, Chang Gung Memorial Hospital, Taipei, Taiwan.
J Med Virol Mar 1990; 30 (3) p181-6, ISSN 0146-6615 Journal Code: I9N
Languages: ENGLISH
Document type: JOURNAL ARTICLE

30
6/3/81 (Item 33 from file: 155)
07302074 90209974

The impact of screening a heterogeneous donor population for alanine aminotransferase and hepatitis B core antibody. Experience at a large Southern California hospital [see comments]
Saxena S; Shulman IA
Interpretive Clinical Pathology Unit, Los Angeles County-University of Southern California Medical Center 90033.
Am J Clin Pathol Apr 1990; 93 (4) p533-7, ISSN 0002-9173
40 Journal Code: 3FK

Comment in Am J Clin Pathol 1990 Apr;93(4):589-91; Comment in: Am J Clin Pathol 1991 Apr;95(4):604-5
Languages: ENGLISH
Document type: JOURNAL ARTICLE

45
6/3/82 (Item 34 from file: 155)
07195348 90102348

Would another test (anti-HCV) have helped? [editorial; comment]
Polesky HF
50 Am J Clin Pathol Jan 1990; 93 (1) p155, ISSN 0002-9173
Journal Code: 3FK
Comment on Am J Clin Pathol 1990 Jan;93(1):79-83
Languages: ENGLISH
Document type: COMMENT; EDITORIAL

5/3/83 (Item 35 from file: 155)
07094599 90001599
Prevalence of antibodies to hepatitis C virus (HCV) in haemophiliacs.
Schramm W; Roggendorf M; Rommel F; Kammerer R; Pohlmann H; Raschofer R;
Burtler L; Deinhardt F
Department of Haemostaseology, University Clinic Innenstadt, University
of Munich, Munchen, Federal Republic of Germany.
Blut Oct 1989, 59 (4) p390-2, ISSN 0006-5242 Journal Code: ABW
Languages: ENGLISH
10 Document type: JOURNAL ARTICLE

6/3/84 (Item 36 from file: 155)
07071195 89373195
Fulminant viral hepatitis in Kuwait.
15 Alkandari S; Mahbut S; Nordenfelt E; al-Nakib B; al-Nakib W
Infectious Diseases Hospital, Kuwait.
Ann Trop Med Parasitol Dec 1988, 82 (6) p555-9, ISSN 0003-4983
Journal Code: 60E
Languages: ENGLISH
20 Document type: JOURNAL ARTICLE

6/3/85 (Item 37 from file: 155)
05861248 89163248
Sequence analysis of the nucleocapsid protein gene of human coronavirus
2829E.
Schreiber SS; Kamahora T; Lai MM
Department of Neurology, University of Southern California, School of
Medicine, Los Angeles 90033.
Virology Mar 1989, 169 (1) p142-51, ISSN 0042-6822 Journal Code:
30EA
Contract/Grant No.: NS18146; AI19244; NS07149
Languages: ENGLISH
Document type: JOURNAL ARTICLE

356/3/86 (Item 38 from file: 155)
06047382 89149382
Transfusion-associated hepatitis C virus (non-A, non-B) infection
[Published erratum appears in Arch Pathol Lab Med 1989 Apr;113(4):368]
Polesky HF; Hanson MR
40 Memorial Blood Center of Minneapolis, MN 55404.
Arch Pathol Lab Med Mar 1989, 113 (3) p232-5, ISSN 0003-9965
Journal Code: 79Z
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

45
6/3/87 (Item 39 from file: 155)
06603827 89248827
Occurrence of indirect markers of non-A, non-B hepatitis (increased
anti-HBc -HBV and -ALT) in altruistic blood donors (letter)]
50 Incidencia de marcadores indirectos de hepatitis NANB (anti-HBc - VHB - y
ALT elevada) en donantes altruistas de sangre.
Lopez Pascual J
Sangre (Barc) Feb 1988, 33 (1) p58-9, ISSN 0036-4355 Journal Code:
U93

Languages: SPANISH
Document type: LETTER

6/3/88 (Item 40 from file: 155)

06569034 88214034

Hepatitis transmission by blood products.

Yap PL

Edinburgh and South East Scotland, Blood Transfusion Service.

J Hosp Infect Feb 1988, 11 Suppl A p166-74, ISSN 0195-6701

Journal Code: ID6

Languages: ENGLISH

Document type: JOURNAL ARTICLE

6/3/89 (Item 41 from file: 155)

106183157 87157157

[Changes in the response time of anti-HBc IgM in a hepatitis B case load.
Diagnostic implications]

Modificazioni nel tempo della risposta delle IgM anti-HBc in una
casistica di epatiti da HBV. Implicazioni diagnostiche.

20 Cremoni L; Buffa D; Saucio F; Bongetta R; Arosio M; d'Amico P

Boll Ist Sieroter Milan 1986, 65 (5) p430-5, ISSN 0021-2547

Journal Code: AKG

Languages: ITALIAN Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

25

6/3/90 (Item 42 from file: 155)

05928830 86229830

Serial transmission of a human non A-non B hepatitis viral strain to
HBV-protected chimpanzees: successive histological and ultrastructural
studies.

Degott C; Trepo C; Durand-Schneider AM; Degos F; Potet F; Feldmann G

Liver Feb 1986, 6 (1) p17-25, ISSN 0106-9543 Journal Code: L74

Languages: ENGLISH

Document type: JOURNAL ARTICLE

35

6/3/91 (Item 43 from file: 155)

05744335 86045335

Unusual viruslike particles in chronic non-A, non-B hepatitis in
childhood.

40 Herrera MI; Vindel AM; Alonso M; Moreno P; Perez Alvarez L; Jara P; Diaz
MC

Ultrastruct Pathol 1985, 8 (2-3) p191-6, ISSN 0191-3123

Journal Code: WMM

Languages: ENGLISH

45 Document type: JOURNAL ARTICLE

6/3/92 (Item 44 from file: 155)

05499403 85115403

Non-A, non-B hepatitis.

50 Fagan EA; Williams R

Semin Liver Dis Nov 1984, 4 (4) p314-35, ISSN 0272-9887

Journal Code: UOB

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW

6/3/93 (Item 45 from file: 155)

05436656 85052656

Contribution of low level HBV replication to continuing inflammatory activity in patients with anti-HBe positive chronic hepatitis B virus infection.

Lok AS; Hadziyannis SJ; Weller IV; Karvountzis MG; Monjardino J; Karayiannis P; Montano L; Thomas HC

Gut Nov 1984, 25 (11) p1283-7; ISSN 0017-5749 Journal Code: FVT

Languages: ENGLISH

10 Document type: JOURNAL ARTICLE

6/3/94 (Item 46 from file: 155)

04854831 83007831

Detection by immunofluorescence of a new "core-like" Ag/Ab system in liver and serum of patients with NANB hepatitis.

Trepo C; Vitvitski L; Hantz O; Chevallier P; Lehman H; Schlaak M; Sepetjan M

Liver Sep 1981, 1 (3) p191-200; ISSN 0106-9543 Journal Code: L74

Languages: ENGLISH

20 Document type: JOURNAL ARTICLE

6/3/95 (Item 47 from file: 155)

04021762 80132762

[Non-A non-B hepatitis virus: demonstration of a double antigenic and structural kinship with hepatitis B virus]

Virus de l'hépatite non A non B: démonstration d'une double parenté antigénique et structurale avec le virus de l'hépatite B.

Trepo C; Vitvitski L; Hantz O; Grimaud JA

C R Seances Acad Sci D Jan 28 1980, 290 (4) p343-6; ISSN 0567-655X

30 Journal Code: C9E

Languages: FRENCH Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

6/3/96 (Item 1 from file: 399)

35 115277951 CA: 115(25)277951y PATENT

Synthetic peptides specific for the detection of antibodies to hepatitis C virus (HCV), diagnosis of HCV infection, and prevention thereof as vaccines

INVENTOR(AUTHOR): Wang, Chang Yi

40 LOCATION: USA

ASSIGNEE: United Biomedical, Inc.

PATENT: European Pat. Appl. ; EP 442394 A2 DATE: 910821

APPLICATION: EP 91101787 (910208) *US 481348 (900216) *US 510153 (900410)

*US 558789 (900726)

45 PAGES: 93 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C07K-007/08A;

C07K-007/10B; C07K-015/00B; G01N-033/576B DESIGNATED COUNTRIES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE

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50

6/3/97 (Item 2 from file: 399)

114200571 CA: 114(21)200571w JOURNAL

A structural protein encoded by the 5' region of the hepatitis C virus genome efficiently detects viral infection

Nakagawa,

Jan, 104

PAGES:

AUTHOR(S): Kato, Nobuyuki; Hijikata, Makoto; Ootsuyama, Yuko; Nakagawa, Masanori; Ohkoshi, Showgo; Shimotohno, Kunitada
LOCATION: Virol. Div., Natl. Cancer Cent. Res. Inst., Tokyo, Japan, 104
JOURNAL: Jpn. J. Cancer Res. DATE: 1990 VOLUME: 81 NUMBER: 11 PAGES: 5092-4 CODEN: JJCREF ISSN: 0910-5050 LANGUAGE: English

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6/3/90 (Item 1 from file: 351)
10000002143 WPI Acc No: 92-009412/02
XRAM Acc No: C92-004034
XRPX Acc No: N92-007237

Non-A, non-B hepatitis virus (NANBV) particles - as vaccines,
immuno-diagnostics and screening agents for NANBV, and to remove NANBV
15 from blood; NON NON VIRUS

Patent Assignee: (OSAU) OSAKA UNIVERSITY

Author (inventor): OKAYAMA H; FUKE I; MORI C; TAKAMIZAWA A; YOSHIDA I

Patent Family:

CC Number	Kind	Date	Week
20 EP 463848	A	920102	9202 (Basic)

Priority Data (CC, No, Date): JP 91138493 (910514); JP 90167466 (900625);
JP 90230921 (900831); JP 90305605 (901109); US 635451 (901220);
JP 91132090 (910508);

Applications (CC, No, Date): EP 91305717 (910625);

25 6/3/90 (Item 2 from file: 351)
003460358 WPI Acc No: 92-09959E/05

XRAM Acc No: C82-E09959

Non-A, non-B hepatitis virus particle useful in vaccines and in
30 immunoassays for the particle antigens or antibodies

Patent Assignee: (BAXT) BAXTER TRAVENOL LABS INC; (CONN-) CONNORT LAB LTD

Author (inventor): COURSADET P L J; MAUPAS P

Patent Family:

CC Number	Kind	Date	Week
35 NO 8200205	A	820121	8205 (Basic)
EP 58676	A	820901	8236
JP 58192556	A	831025	8348
US 4464474	A	840807	8434
EP 58676	B	861008	8641
40 DE 3175439	G	861113	8647
IT 1138449	B	860917	8612
CA 1261773	A	890926	8945

Priority Data (CC, No, Date): US 167282 (800709); JP 8258933 (820407); CA
400069 (820331);

40 Applications (CC, No, Date): EP 81901986 (810624);

?s s2 and immunodominant

624 S3
50 2314 IMMUNODOMINANT
S7 3 S3 AND IMMUNODOMINANT
76 7/3/1-3

616363

7/3/1 (Item 1 from file: 155)
 07959601 92096601
 IgM antibody response in acute hepatitis C viral infection.
 Clemens JM; Taskar S; Chau K; Vallari D; Shih JW; Alter HJ; Schleicher JD
 & Minns LT
 Abbott Laboratories, Abbott Park, IL 60064.
 Blood (UNITED STATES) Jan 1 1992, 79 (1) p169-72, ISSN 0006-4971
 Journal Code: A88
 Languages: ENGLISH
 10 Document type: JOURNAL ARTICLE

7/3/2 (Item 2 from file: 155)
 07875081 92013081
 Identification of an immunodominant B cell epitope on the hepatitis C
 10virus nonstructural region defined by human monoclonal antibodies.
 Cerino A; Mondelli MU
 Istituto di Clinica delle Malattie Infettive, I.R.C.C.S. Policlinico San
 Matteo, University of Pavia, Italy.
 J Immunol Oct 15 1991, 147 (8) p2692-6, ISSN 0022-1767
 20Journal Code: IFB
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE

7/3/3 (Item 3 from file: 155)
 027752409 91271409
 Identification of an immunodominant epitope within the capsid protein of
 hepatitis C virus.
 Nasoff MS; Zebedee SL; Inchauspe G; Prince AM
 Pharmacia Genetic Engineering, Inc., La Jolla, CA 92037.
 30 Proc Natl Acad Sci U S A Jun 15 1991, 88 (12) p5462-6, ISSN 0027-8424
 Journal Code: PVE
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE

?ds

35

Set	Items	Description
S1	2473	NON? (W) HEPATITIS OR (NANB?) OR (HCV)
S2	568407	ANTIGEN?
403	624	S1 AND S2
S4	201124	CORE
S5	129	S3 AND S4
S6	99	RD S5 (unique items)
S7	3	S3 AND IMMUNODOMINANT

45log y

30mar92 09:56:42

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PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1992.

Application or Docket Number

08/272271

CLAIMS AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA
BASIC FEE		
TOTAL CLAIMS	9 minus 20 =	* 0
INDEPENDENT CLAIMS	1 minus 3 =	* 0
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY

OR

OTHER THAN
SMALL ENTITY

RATE	FEE
	\$355.00
x\$11=	
x 37=	
+115=	
TOTAL	

OR

RATE	FEE
	\$710.00
x\$22=	
x 74=	
+230=	
TOTAL	710.00

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA
	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR		
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY

OR

OTHER THAN
SMALL ENTITY

RATE	ADDI- TIONAL FEE
x\$11=	
x 37=	
+ 115=	
TOTAL	

OR

RATE	ADDI- TIONAL FEE
x\$22=	
x 74=	
+ 230=	
TOTAL	

AMENDMENT B	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA
	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR		
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

TOTAL
ADDIT. FEE

OR
TOTAL
ADDIT. FEE

RATE	ADDI- TIONAL FEE
x\$11=	
x 37=	
+ 115=	
TOTAL	

OR

RATE	ADDI- TIONAL FEE
x\$22=	
x 74=	
+ 230=	
TOTAL	

AMENDMENT C	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA
	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR		
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

TOTAL
ADDIT. FEE

OR
TOTAL
ADDIT. FEE

RATE	ADDI- TIONAL FEE
x\$11=	
x 37=	
+115=	
TOTAL	

OR

RATE	ADDI- TIONAL FEE
x\$22=	
x 74=	
+230=	
TOTAL	

If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

If the Highest Number Previously Paid For in THIS SPACE is less than 20, enter "20".

If the Highest Number Previously Paid For in THIS SPACE is less than 3, enter "3".

If the Highest Number Previously Paid For (Total or Independent) is the highest number found in the appropriate box in column 1.

Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE



DATE _____

1ST EXAMINER *Dr. A. Smith*

DATE 8/3/94

APPLICATION NUMBER

08/272271

TYPE
APPL

FILING DATE .
MONTH **DAY** **YEAR**

SPECIAL HANDLING

GROUP
ART UNIT

CLASS

SHEETS OF DRAWING

TOTAL CLAIMS

INDEPENDENT CLAIMS

SMALL ENTITY?

FILING FEE

**FOREIGN
LICENSES**

ATTORNEY DOCKET NUMBER

CONTINUITY DATA

CONT	STATUS
CODE	CODE

**PARENT APPLICATION
SERIAL NUMBER**

PCT APPLICATION SERIAL NUMBER

**PARENT PATIENT
NUMBER**

**PARENT FILING
DATE**

[illegible]

P	C	T	/														
R	C	T	/						/								
P	C	T	/						/								
P	C	T	/						/								
P	C	T	/						/								
P	C	T	/						/								

[illegible]

**FOREIGN
PRIORITY
CLAIMED**

COUNTRY
CODE

PCT/FOREIGN APPLICATION SERIAL NUMBER

**FOREIGN
FILING DATE**
MONTH DAY YEAR

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